17 Myeloproliferative neoplasms

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The online version of this chapter contains an educational multimedia component on JAK-STAT activation by recurrent mutations leading to myeloproliferation.

Conflict-of-interest disclosure: Angela Fleischman: membership on advisory board: PharmaEssentia, CTI, BMS. Kristen Pettit: membership on advisory board: PharmaEssentia, Kura Oncology.

Off-label drug use: Interferon for MPNs.

Introduction

The myeloproliferative neoplasms (MPNs) are a phenotypically diverse group of stem cell-derived clonal disorders characterized by myeloid proliferation. MPNs are largely classified according to their molecular drivers: BCR/ABL+ CML, BCR/ABL- classical MPNs (polycythemia vera [PV], essential thrombocythemia [ET], and myelofibrosis) driven by activated JAK/STAT pathway signaling, and other MPNs (chronic neutrophilic leukemia [CNL], chronic eosinophilic leukemia [CEL], other eosinophilic disorders) with miscellaneous drivers (Table 17-1). MPNs share several clinical and laboratory features, including a pronounced symptom burden that impacts quality of life, a thrombotic tendency, extramedullary hematopoiesis (EMH) resulting in organomegaly (hepatomegaly or splenomegaly), the potential to develop progressive marrow fibrosis. Fibrosis results in bone marrow failure and risk of transformation to acute myeloid leukemia (AML), also known as MPN-blast phase (MPN-BP).

In recognition of these shared clinical, laboratory, and histological features, William Dameshek first used the term *myeloproliferative disorders* in 1951 to encompass essential thrombocythemia, polycythemia vera, and primary myelofibrosis (PMF). Dameshek also speculated on a shared pathogenesis, owing to the presence of a "myelostimulatory factor." In 2005, Dameshek's hypothesis was confirmed after the discovery of the activating Janus kinase (*JAK2*) V617F mutation. The discovery ushered in a new era of exploration and understanding of these complex disorders. The molecular genetic landscape in Dameshek's classical MPNs has since become well characterized. Activating point mutations of *JAK2* are observed in almost all patients with PV, and in a significant proportion of patients with ET and PMF. Calreticulin (*CALR*) mutations are observed in substantial proportions of patients with *JAK2* V617F–negative ET and myelofibrosis (MF). Somatic-activating *JAK2* exon-12 mutations and myeloproliferative-leukemia (*MPL*) mutations are less frequently identified mutations in patients with *JAK2* V617F–negative PV and ET/MF, respectively. One of these 3 so-called "driver" mutations in *JAK2*, *CALR*, and *MPL* is found in the vast majority of patients with ET, PV, or MF. All 3 molecular states result in activation of the JAK-STAT signaling pathway. Driver mutations are usually mutually exclusive; however, rare patients do harbor 2 separate MPN driver mutations. Rare cases lacking mutations in these 3 driver genes are termed "triple-negative" MPNs.

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Table 17-1 2016 WHO classification of MPNs and related disorders

MPNs
CML, *BCR-ABL1*-positive
CNL
PV
PMF
PMF, prefibrotic/early-stage
PMF, overt fibrotic stage
ET
CEL-NOS
MPN, unclassifiable
Systemic mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1* or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: myeloid/lymphoid neoplasms with PCM1-JAK2

Other MPNs have been found to harbor consistent molecular genetic abnormalities as well. Mutations in *CSF3R*, which encode the granulocyte colony-stimulating factor receptor, have been found in most patients with chronic neutrophilic leukemia. In addition, systemic mastocytosis (SM), now considered distinct from the classical MPNs, is frequently associated with somatic mutations in *KIT* (eg, *KIT* D816V). Finally, myeloid neoplasms with eosinophilia are characterized by rearrangements involving platelet-derived or fibroblast-growth-factor receptors (*PDGFRA*, *PDGFRB*, *FGFR1*), or *JAK2* point mutations or translocations.

As a result of these molecular discoveries, Dameshek's myeloproliferative disorders are now classified by the World Health Organization (WHO) as clonal, neoplastic entities, reflected in the current terminology of "MPNs" (Table 17-1). Without question, these molecular genetic abnormalities aid the clinician's diagnostic capabilities, prognostic assessments, and therapeutic choices. However, these mutations do not replace, but rather complement, clinical, laboratory, and histological findings that allow for diagnosis of the distinct MPN subtype. Establishing a diagnosis with accuracy can be challenging given that the MPNs discussed here can mimic one another. Yet, diagnosis is paramount to treatment given the prognostic and therapeutic implications. In this chapter, the impact from driver mutations, as well as the diagnosis, clinical features, treatment, and prognosis of classical and atypical MPNs are reviewed.

Driver mutations

JAK2 mutations

A watershed moment in the understanding of the MPNs arose in 2005 when an activating point mutation in the *JAK2* gene, *JAK2* V617F, was discovered in patients with ET, PV, and MF (Table 17-2). JAK2 is an intracellular signaling molecule coupled to several cell surface hematopoietic growth factor receptors that lack intrinsic kinase domains, including the erythropoietin (EPO) receptor, GCSF receptor, and the thrombopoietin receptor (c-MPL). The *JAK2* V617F point mutation is thought to result in loss of the pseudokinase domain's (JH2) inhibitory control of the kinase domain (JH1) (see video on *JAK2*, *MPL*, and *CALR* mutations in online edition).

Table 17-2 Somatic mutations seen in patients with ET, PV, and MF

Gene name	Mutation effect	PV (%)	ET (%)	MF (%)
JAK2 (V617F)	JAK/STAT signaling	95-97	50-60	50-60
JAK2 exon-12	JAK/STAT signaling	1-2	0	0
CALR	JAK/STAT signaling	0	25	30
MPL	JAK/STAT signaling	0	3-5	5-10
CBL	JAK/STAT signaling	Rare	Rare	5-10
SH2B3/LNK	JAK/STAT signaling	1-2	3-6	3-6
ASXL1	Epigenetic modification	2	2-5	10-35
EZH2	Epigenetic modification	1-2	1-2	7-10
IDH1/2	Epigenetic modification	1-2	1-2	5-6
DNMT3A	Epigenetic modification	5-10	1-5	8-12
TET2	Epigenetic modification	10-20	5	10-20
SF3B1	mRNA splicing	2	2	5
SRSF2	mRNA splicing	Rare	Rare	5-17
U2AF1	mRNA splicing	Rare	Rare	16
ZRSR2	mRNA splicing	Rare	Rare	1
TP53	DNA repair	Rare	Rare	Rare

mRNA, messenger RNA.

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The consequence is constitutive, ligand-independent activation of the JAK-STAT pathway. JAK/STAT overactivation promotes myeloid progenitor proliferation and differentiation, which accounts for the phenotype of erythrocytosis, leukocytosis, and/or thrombocytosis often observed in MPNs. *JAK2*V617F is present in ~95% of PV cases and can be heterozygous or homozygous in at least one-third of PV cases because of the acquired uniparental disomy of the region, including the mutated gene on chromosome 9p24.

Analysis of *JAK2* V617F–negative PV patients led to the identification of acquired-activating mutations in exon-12 of *JAK2*. Unlike the more pleiotropic *JAK2* V617F allele, which is seen in a spectrum of myeloid malignancies, *JAK2* exon-12 mutations are found in *JAK2* V617F–negative PV and most often are identified in cases with isolated erythrocytosis. *JAK2* V617F is identified in about 50% to 60% of ET and PMF cases. Noncanonical, germline *JAK2* variants have been identified in patients with "triple-negative" ET and in families (*JAK2* V617I and *JAK2* R564Q) with hereditary thrombocytosis.

MPL

After discovery of *JAK2*V617F, much effort was expended in identifying other mutations that are important in the diagnosis and pathogenesis of MPNs (Table 17-2). The next recurrent MPN mutations described were somatic-activating mutations in the gene encoding the thrombopoietin receptor (*MPL*). *MPL* mutations are seen in 3% to 5% of patients with ET, and 5% to 10% of those with MF but are not seen in PV. *MPL* mutations (W515, S505) also lead to ligand-independent JAK-STAT activation and, predominantly, megakaryocyte proliferation. Noncanonical germline and somatic *MPL* mutations have been identified in patients thought to have "triple-negative" ET. Germline *MPL* mutations that lead to constitutive overexpression of the gene product have also been identified in several kindreds known to have the rare entity of hereditary thrombocytosis.

CALR

In late 2013, mutations in the calreticulin gene (*CALR*) were identified and are now known to be present in 25% to 30% of all ET and MF patients (Table 17-2). Mutations in *CALR* have been found infrequently in other myeloid neoplasms, including myelodysplastic syndrome (MDS) and MPN/MDS overlap syndromes. The mutations in *CALR* occur in the terminal exon-9 of the gene and result in a +1-base-pair frameshift in the reading frame. The 2 most common types of mutations include a 52-base frameshifting deletion (type 1/type 1-like) or a 5-base-pair insertion (type 2/type 2-like), which leads to a novel peptide sequence. Recent work by several laboratories demonstrates that the mutant *CALR* binds MPL, which leads to activation of the JAK-STAT pathway. There are phenotypic and prognostic implications regarding the presence of the *CALR* mutation, as discussed in the ET and MF sections.

KIT D816V

KIT is the protein tyrosine-kinase receptor for stem cell factor (SCF) and is expressed by mast cells. Most cases of systemic mastocytosis (SM) are associated with somatic-activating point mutations of *KIT*. The most common point mutations, found in ~90% of SM patients, result from a Val for Asp substitution at codon 816 (D816V). The point mutations result in ligand-independent activation of KIT, which promotes mast cell proliferation and survival. A *KIT* juxtamembrane mutation in codon 560 also has been described in a human mast cell line called HMC-1 and rarely is found in SM. Rare juxtamembrane and transmembrane variants of *KIT* point mutations also have been described, as well as alternative *KIT* D816 codon mutations such as D816Y/H/F/I.

CSF3R

In 2013, understanding of the genetic basis of CNL was improved with the demonstration of mutations in the gene encoding the receptor of colony-stimulating factor 3 (*CSF3R*). Maxson et al hypothesized that patients with CNL, as well as the MDS/MPN overlap syndrome called atypical chronic myeloid leukemia (CML), would harbor oncogenes that would be sensitive to kinase inhibition. Using a deep sequencing approach with coverage of 1862 genes, they found that 16 of 27 (59%) harbored *CSF3R* mutations, including 8 of 9 with CNL. Two types of mutations were observed: membrane proximal mutations (point mutations in the extracellular or transmembrane region) and truncation mutations (frameshift or nonsense mutations that truncate the cytoplasmic tail of CSF3R). The influence on downstream signaling pathways and, subsequently, sensitivity to kinase inhibition, differed depending on the type of mutation: truncation mutations activated the SRC family-TNK2 kinase signaling and showed sensitivity to dasatinib, whereas proximal mutations activated the JAK-STAT pathway. As proof of concept, a patient carrying a JAK-STAT–activating *CSF3R* mutation experienced clinical improvement in neutrophilic leukocytosis

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and thrombocytopenia when treated with ruxolitinib. In a murine model, transplantation with the most common mutation in CNL, *CSF3R* T618I, recapitulated an aggressive MPN characterized by granulocytic proliferation and infiltration of the liver and spleen. JAK inhibition with ruxolitinib reduced the leukocyte count and spleen weight. Subsequently, in another study, 10 of 12 (83%) WHO-defined CNL cases were found to carry *CSF3R* mutations.

Growth factor rearrangements: *PDGFRA, PDGFRB,* and *FGFR1*

The *PDGFRA* gene, located on the long arm of chromosome 4 (4q12), has been implicated in the chronic eosinophilic syndromes because of a cryptic interstitial deletion at 4q12, leading to the juxtaposition and in-frame fusion of *FIP1L1* and *PDGFRA*. This deletion evades standard cytogenetic banding techniques, which explains why most cases of chronic eosinophilic leukemia apparently have a normal karyotype. Expression of *FIP1L1-PDGFR* transformed a murine hematopoietic cell line, was constitutively active in these cells, and led to increased STAT5 phosphorylation. Similar transforming properties were noted when *STRN-PDGFRA* or *ETV6-PDGFRA* fusion genes were transfected into murine hematopoietic cell lines. Several other partner genes have been implicated in the pathogenesis of *PDGFRA*-related neoplasms, including *BCR*, *ETV6*, *KIF5B*, and *CDK5RAP2*.

The *PDGFRB* gene is located on the long arm of chromosome 5 (5q31–33). In 1994, Golub et al were the first to characterize the t(5;12)(q31-q33;p13) translocation involving *ETV6* (12p13) and *PDGFRB* (5q33). Since then, more than 30 partner genes have been identified to collaborate in the development of *PDGFRB*-related neoplasms.

The molecular consequences of *FGFR1* rearrangements are remarkably well-described for such an unusual disorder. In all *FGFR1*-related neoplasms, the N-terminal partner containing self-association motif is fused to the C-terminal tyrosine-kinase domain of *FGFR1*. These fusion genes (*ZNF198FGFR1*), when expressed in primary murine hematopoietic cells, cause an MPN that recapitulates the human MPN phenotype. Furthermore, these constitutively active *FGFR1* fusion genes activate downstream effector molecules, such as PLC-g, STAT5, and PI3K/AKT.

Additional MPN mutations

A spectrum of somatic mutations in genes involved in various cellular processes has also been recurrently identified in MPNs (Table 17-2), which includes genes that regulate DNA methylation (*TET2*, *DNMT3A*, *IDH1/IDH2*), histone modification (*ASXL1*, *EZH2*), RNA splicing (*SF3B1*, *U2AF1*, *ZRSR2*, *SRSF2*), signal transduction (*LNK*, *CBL*, *NRAS*), and DNA repair (*TP53*). Identification of such mutations indicates clonality in those with "triple-negative" ET or MF and can be diagnostically useful. Prognostic implications of these mutations are discussed in the respective disease-associated chapters.

Additional contributions to disease pathogenesis

The presence of the *JAK2* V617F mutation across all subtypes of MPN, as well as *CALR* and *MPL* in both ET and MF, raises the question of what other factors contribute to the phenotypic heterogeneity within different MPNs that share the same mutation. Differences in allele burden, downstream intracellular signaling, bone marrow microenvironment, epigenetic factors, host genetic background, age, sex, acquisition of other molecular mutations (including the order of acquisition), and the hematopoietic progenitor tissue type targeted by the mutation can all influence phenotype. A germ line haplotype (46/1, GGCC) at the 3′ region of *JAK2* also has been associated with a 3- to 4-fold increased risk of developing a *JAK2* V617F mutant or *MPL* mutant MPN. *TERT* gene polymorphisms and other germ line predisposition loci affecting a multitude of cellular processes also contribute to an increased risk of MPN.

Overlapping clinical features among the classical *BCR-ABL1*–negative MPNs

MPNs subtypes exhibit significant overlap in presentation, symptoms, physical examination findings, laboratory findings, and clinical consequences. A comparison of disease features is presented in Table 17-3.

Laboratory features

Early in their course, most MPNs exhibit characteristic cytoses, including any combination of erythrocytosis (PV), thrombocytosis (ET, and often PV), and leukocytosis (PV, ET, and often MF). Later in the disease course, a "burnt out" state with marrow fibrosis and more frequent cytopenias can occur. Signs of increased cell turnover, such as increased lactate dehydrogenase (LDH) and uric acid levels, are variably present in ET and PV but more common in MF.

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Table 17-3 Laboratory, physical findings, and symptoms at presentation

Feature	PV	ET	MF (PMF/ post-ET/ PV MF)
Laboratory features			
Erythrocytosis	+++	Absent	Absent
Leukocytosis	Variable	Variable	Variable
Thrombocytosis	Variable	+++	Variable
Leukoerythroblastosis	Absent	Absent	+++
Decreased serum erythropoietin	+++	Variable	Absent
Elevated lactate dehydrogenase	Variable	Absent	Common
Hyperuricemia	Uncommon	Uncommon	Variable
Physical findings			
Splenomegaly	+	+	+++
Hepatomegaly	Absent	Absent	+
Plethora	++	Absent	Absent
Pallor	Absent	Absent	Variable
Disease-related symptoms (MPN-10)*			
Fatigue	84%	85%	94%
Early satiety	56%	60%	74%
Abdominal discomfort	48%	48%	65%
Inactivity	54%	60%	76%
Problems with concentration	58%	62%	68%
Night sweats	47%	52%	63%
Pruritus	46%	62%	52%
Bone pain	45%	48%	53%
Fever	17%	19%	24%
Weight loss	28%	33%	47%
Additional presenting features			
Erythromelalgia	+	++	Absent
Thrombosis	Variable	Variable	Variable
Hemorrhage	Variable	Variable	Variable
Portal hypertension	Variable	Variable	Variable

*See Geyer HL, Mesa RA, *Blood*. 2014;124:3529-3537.

+ to +++: occasional to very common.

Physical examination findings

Extramedullary hematopoiesis is common in MPNs, and results from dysregulated trafficking of hematopoietic cells to organs outside of the bone marrow and subsequent proliferation in those environments. Clinically, this results in splenomegaly (which can be massive, particularly in the MF stage) and often hepatomegaly (again, generally in later stages of the disease). It is important to note that physical examination findings may be largely absent even in extremely symptomatic patients.

Symptoms

MPNs are notorious for inflicting bothersome symptoms that impair quality of life; although, symptoms can vary significantly among patients and can change throughout the disease course. In general, symptoms may be inflammatory cytokine-related, vascular in origin, and/or related to organomegaly. Fatigue is the most commonly-reported symptom across the MPN spectrum and the most burdensome for patients. Other cytokine-related symptoms include weight loss, bone pain, fever, and night sweats. Microvascular or vasomotor symptoms may include headaches, visual disturbances, neuropathic symptoms, or erythromelalgia (burning pain in the hands or feet, usually accompanied by erythema and swelling). Hepatomegaly or splenomegaly can cause abdominal pain, early satiety, and weight loss. In addition, it is important to recognize cognitive and psychiatric manifestations of MPNs. Concentration issues ("brain fog"), depression, and anxiety are all common.

The constellation of MPN-related symptoms has been quantified and can be measured and tracked with validated MPN-specific, patient-reported outcome tools. One such tool is the MPN-10 score (also known as the MPN Symptom Assessment Form Total Symptom Score or MPN-SAF TSS). As part of the MPN-10 score, patients rank 10 common disease-related symptoms on a severity scale of 1 to 10, which are then added together (the 10 components are listed in Table 17-3). This quantification of symptoms can then be followed serially and used to assess for disease progression or response to treatment.

Vascular events

Vascular events are prevalent in ET, PV, and MF, peaking around the time of diagnosis and plateauing by the end of the first decade of the disease. Large-vessel thromboses may be venous (deep vein thromboses or pulmonary emboli) or arterial (myocardial infarction, cerebrovascular event, or other thromboses) and have the propensity to involve unusual sites such as portal, splenic, or mesenteric veins. Thromboses are often the presenting feature of MPNs; Budd-Chiari syndrome, particularly resulting intraabdominal clots, should prompt a workup for an MPN. Microvascular disturbances described previously are less dangerous, but can significantly impact quality of life. Bleeding is less common than thrombosis, but it is present in each MPN with multifactorial etiologies.

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Polycythemia vera

CLINICAL CASE

A 60-year-old male violinist presented with intractable pruritus. The patient's general physician noticed multiple skin excoriations but no rash. The patient was prescribed antihistamines and steroid cream. A week later, he returned complaining of persistent pruritus (especially after hot showers), facial flushing, and painful erythematous swelling of his fingers. Physical examination revealed erythematous swelling of both hands, multiple skin excoriations, and palpable splenomegaly. Vital signs, including oxygen saturation, were within normal limits. A complete blood count (CBC) showed white blood cells (WBCs) = 12×10^9/L, Hemoglobin (Hgb) = 17 g/dL, mean corpuscular hemoglobin = 85 fL, and platelet count = 830×10^9/L. Additional blood tests showed a serum erythropoietin level of 2 U/L (normal, 7 to 20 U/L) and the presence of a *JAK2* V617F mutation. The patient underwent therapeutic phlebotomy and started on aspirin (81 mg by mouth once daily) with improvement in pruritus and erythematous swelling of both hands.

Introduction

PV is the most common MPN in the United States, with an annual incidence rate of roughly 1.1 cases per 100,000 persons per year, a slight male predominance, and a median age at diagnosis in the seventh decade (~5% of cases occur in those <40 years old). Radiation exposure and, rarely, environmental or toxic factors have been linked to the disease. The hallmark feature of PV is increased red blood cell production, with resulting clinical consequences including thromboses, constitutional symptoms, microvascular symptoms, splenomegaly, and potential for progression to post-PV MF or transformation to MPN-BP.

Diagnosis

Differential diagnosis

The differential diagnosis for erythrocytosis is broad, and includes primary causes (ie, PV), relative causes (ie, intravascular volume depletion), or secondary causes (ie, excess erythropoietin production or hypoxia) (Table 17-4). An elevated hematocrit may result from either an increase in the total red cell mass (absolute) or a decrease in the total plasma volume (relative). The latter condition usually is because of moderate to severe intravascular dehydration, such as dehydration attributed to diuretics, diarrhea, or loss of fluid into third spaces. In some cases (2.5% of healthy patients based on statistical distributions of laboratory ranges), an increased hematocrit may represent a normal variant.

Table 17-4 Causes of secondary erythrocytosis

Congenital
Mutant high oxygen–affinity hemoglobin
Congenital low 2,3-bisphosphoglycerate
Autonomous high-EPO production (including Chuvash-type polycythemia associated with *VHL* mutations)
Autosomal-dominant polycythemia (including truncating EPO receptor mutations)
HIF2A (*EPAS1*) mutation
Proline hydroxylase (*EGLN1*) mutation
Congenital methemoglobinemia
Acquired
Arterial hypoxemia High altitude Cyanotic-congenital heart disease Chronic lung disease Sleep apnea and hypoventilation syndromes
Other causes of impaired tissue oxygen delivery Smoking Carbon monoxide poisoning Acquired methemoglobinemia
Renal lesions Renal cysts Hydronephrosis Renal artery stenosis Renal transplantation
Miscellaneous tumors Parotid tumors Cerebellar hemangiomas Hepatoma Renal cell carcinoma Uterine myomata Cutaneous leiomyomata Bronchial carcinoma Ovarian tumors Adrenal tumors Meningiomas Pheochromocytomas
Drugs and chemicals Androgens ESAs (eg, epoetin alfa or darbepoetin alfa) Nickel, cobalt

Adapted from Pearson TC, Messinezy M, *Pathol Biol (Paris)*. 2001;49:170-177.

A history of smoking or occupational exposure to hydrocarbon fumes may lead to arterial blood gas and carboxyhemoglobin determinations. Lung disease, cardiac disease, or sleep apnea should be considered. Physicians should ask about androgen replacement therapy or abuse. Inappropriate EPO production can occur in the setting of certain EPO-producing tumors. Absolute erythrocytosis may occur in up to 15% of renal transplant patients. When treatment is required, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are often

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effective. Some patients can have concurrent primary and secondary causes, and the presence of the *JAK2* V617F allele supports the identification of PV even in patients with concomitant secondary polycythemia.

Primary familial and congenital erythrocytosis is usually autosomal-dominant and most commonly associated with low-serum EPO levels. Approximately 10% of such cases have been linked to germline truncating mutations of the EPO receptor that abrogate an important inhibitory domain and lead to constitutive EPO receptor signaling. In contrast, normal or high-EPO levels are found in patients with Chuvash-type congenital polycythemia because of abnormalities in cellular oxygen sensing. This autosomal-recessive disorder was first recognized among the population of the Chuvash region of Russia and is associated with a high risk of thrombotic and hemorrhagic complications. Sporadic cases of Chuvash-type polycythemia with homozygous or compound heterozygous inheritance patterns subsequently have been identified among other ethnic groups. These patients have mutations involving a region of the *von Hippel-Lindau* (*VHL*) gene that is distinct from the autosomal-dominant *VHL* mutations associated with von Hippel-Lindau syndrome. The Chuvash-type *VHL* mutations impair the function of the *VHL* gene product to facilitate degradation of hypoxia-inducible factor 1 (HIF1), an oxygen-responsive transcriptional factor that upregulates EPO expression. More recent studies of families with autosomal-dominant heritable erythrocytosis have identified germ line mutations in the *HIF2A* gene that lead to defective oxygen sensing and resultant polycythemia. These mutations are heterozygous and result in dysregulation of the HIF transcriptional complex. Another autosomal-dominant familial polycythemia is caused by germ line mutations in *proline hydroxylase domain 2* (*PHD2*). *PHD2* is an Fe(II)– and 2-oxoglutarate-dependent oxygenase that hydroxylates HIF2A to allow it to be targeted for ubiquitination and degradation by VHL. Finally, high-affinity hemoglobins may be found in those with a family history of erythrocytosis. Such patients may be evaluated by the identification of a low P50 value on hemoglobin-oxygen-affinity curve testing.

Distinction between PV and secondary erythrocytoses is important both for prognosis and treatment because secondary polycythemia does not carry a risk of leukemic transformation or fibrotic progression and has a lower/unclear risk of thrombosis. Furthermore, phlebotomy can be harmful when erythrocytosis is compensatory (ie, in those with cyanotic-congenital heart disease, chronic hypoxia, or high-affinity hemoglobins). Phlebotomy is only necessary in secondary polycythemia, indicated to decrease blood viscosity and improve oxygenation when symptoms occur prophylactically. There is no established hematocrit goal in secondary erythrosis.

Diagnostic criteria for PV

The WHO revised diagnostic criteria for PV in 2016 (Table 17-5). Compared with the 2008 revision, the most significant change is in the lowering of the hemoglobin/hematocrit threshold. This change was made based on concerns that the prior Hgb/Hematocrit (Hct) 2008 criteria had lost sensitivity in striving for extreme specificity. Prior studies supporting this change suggested that cohorts of *JAK2*-positive ET were reclassified as having PV when additional testing, such as red cell mass studies or bone marrow biopsies, were performed. Another study of those with "masked PV" (*JAK2* mutations and characteristic bone marrow features but Hgb values below the 2008 threshold) distinguished this group from those with ET if the Hgb values were ≥16 g/dL or 16.5 g/dL in women and men, respectively. The identification of *JAK2* V617F or *JAK2* exon-12 mutations remains a major criterion (Table 17-5). A bone marrow biopsy is now required as a major criterion for diagnosis. Characteristic bone marrow features include panmyelosis, an increase in pleomorphic megakaryocytes (ranging from small to medium to large sizes), and absent iron stores (Figure 17-1). The bone marrow biopsy results can be deferred per WHO if prior WHO 2008 Hgb/Hct thresholds are observed (Hgb >16.5 g/dL and 18.5 g/dL in women and men, respectively) in the setting of other major criteria. The bone marrow can be prognostic, as up to 20% may have grade 1 fibrosis at diagnosis, which predicts for a higher rate of overt fibrotic progression. Additionally, at diagnosis, ~15% of karyotypes from PV patients contain nonrandom chromosomal abnormalities, which may be prognostically important. The only remaining minor criterion is a subnormal EPO level,

Table 17-5 WHO 2016 PV diagnostic criteria

Major	1. Hemoglobin >16.5 g/dL in men (or Hct >49%), >16.0 g/dL in women (or Hct >48%), or >25% increase in red cell mass
	2. Bone marrow biopsy results with characteristic features (panmyelosis, pleomorphic megakaryocytes)
	3. Presence of *JAK2*V617F or *JAK2* exon-12 mutation
Minor	Serum erythropoietin level below the reference range for normal
Diagnosis	All 3 major criteria or first 2 major criteria and the minor criterion

Adapted from Arber DA et al, *Blood*. 2016;127(20):2391-2405.

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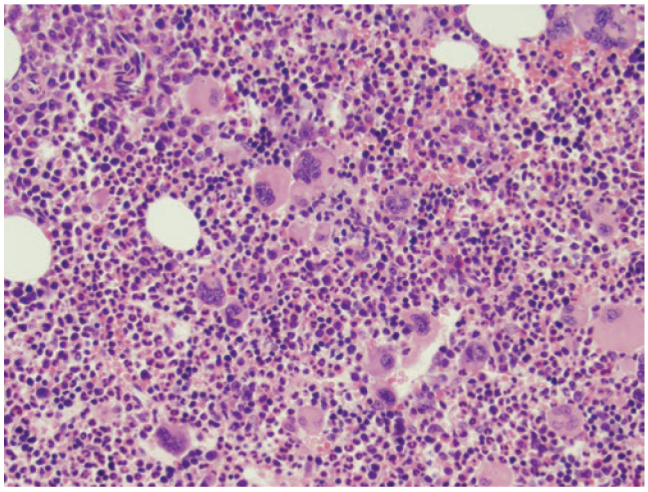

Figure 17-1 PV bone marrow biopsy. The core shows a hypercellular marrow for age with panmyelosis (proliferation of the erythroid, granulocytic, and megakaryocytic lineages). Megakaryocytes are increased and include frequent hyperlobated forms. Source: ASH Image Bank/Elizabeth L. Courville.

which is observed in ~85% of patients. Serum EPO levels within the normal range also occur in PV, especially when EPO levels are not measured until after the patient has undergone initial therapeutic phlebotomy.

Disease course and prognosis

In the short term, patients with PV have a risk of thrombotic events, both venous and arterial, as well as risk of hemorrhagic events. Additionally, the symptomatic burden may be bothersome. The constitutional/inflammatory, vasomotor, and splenomegaly-related symptoms seen across MPN subtypes are all common in patients with PV. Aquagenic pruritus, or diffuse itching after exposure to warm water, is common and relatively specific to PV. Progression to fibrosis or leukemia is possible, typically later in the disease course.

Vascular events in PV

Vascular events are a major cause of morbidity and mortality in patients with PV. Data from the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study revealed a thrombotic complication rate of 5.5 events per 100 patients per year at a median follow-up time of 2.7 years. Two-thirds of those events were arterial, and one-third were venous. The risk of a thrombotic complication in the ECLAP cohort was increased in PV patients >65 years old (hazard ratio [HR], 8.6) with a history of prior thrombosis (HR, 4.85) or >65 years old and with thrombosis (HR, 17.3). Accordingly, age and thrombosis history represent the major factors used to assess thrombotic risk in PV patients. In addition, cardiovascular morbidity and mortality in PV were linked significantly to smoking, diabetes, and congestive heart failure. Subsequent multicenter retrospective studies and a prospective randomized study reported overall event rates near 2.6% to 2.7% per year, possibly reflecting earlier diagnosis and more aggressive treatment approaches. In a population-based cohort study, the highest rate-ratios for thrombosis in all groups were observed shortly after diagnosis but persisted through follow-up.

The cause of thromboses in PV is multifactorial. Beyond age and prior thrombosis history, there is a contribution from uncontrolled erythrocytosis, and lowering hematocrit has shown to be protective. In addition, there are contributions from cardiovascular risk factors, including hypertension, and differences in risk according to sex (venous events more likely in women). Platelet and granulocyte activation (as well as leukocytosis) likely contribute to the pathogenesis as well. Thrombocytosis itself does not associate with thrombosis risk but, rather, bleeding risk. Increased *JAK2* allelic burden may also contribute. In keeping with contributions from acquired somatic mutations, clonal hematopoiesis itself associates with an increase in cardiovascular risk, which is mediated through inflammatory stress. Numerous other potential biomarkers have been reported but are not used routinely in clinical practice.

Bleeding rates are lower than thrombosis rates, and are also multifactorial in etiology. In some cases, particularly those with extreme thrombocytosis, acquired von Willebrand's disease may be present. Antiplatelet and anticoagulant use can increase risk, and bleeding event rates are near 8% following surgery.

Post-PV MF

Patients with PV can experience disease progression to postpolycythemic MF (post-PV MF) or transformation of the disease to acute myeloid leukemia, also known as MPN-blast phase (MPN-BP) (Table 17-6). Post-PV MF typically develops in individuals with longstanding disease duration (>10 years). Indications of disease progression include loss of phlebotomy requirement; progressive anemia; new thrombocytopenia; increasing leukocytosis or progressive leukopenia; progressive splenomegaly; a change from baseline symptoms, including weight loss, night sweats, bone pain, and/or fever; and increasing marrow fibrosis upon biopsy results. Risk factors for MF progression include advanced age at diagnosis; disease duration; leukocytosis ($\geq 15 \times 10^9$/L) at diagnosis; baseline bone marrow fibrosis; an increased *JAK2* allelic burden (>50%); and possibly additional somatic mutations, including *ASXL1*, *IDH*, and *SRSF2*.

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Table 17-6 Criteria of progression of PV and ET

Type of progression	Criteria	Details
Post-ET or post-PV myelofibrosis (both major criteria and 2 minor criteria required)	Major criteria	Documentation of a previous WHO diagnosis of ET or PV
		Bone marrow fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale)
	Minor criteria	PV: anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment of erythrocytosis (PV)
		ET: anemia and a 2-g/dL decrease from baseline Hgb
		A leukoerythroblastic peripheral blood picture
		ET: increased LDH above reference range
		Increasing splenomegaly defined as either an increase in palpable splenomegaly by 5 cm (from the left costal margin) or the appearance of newly palpable splenomegaly
		Development of 1 of 3 constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fevers >37.5 °C
MPN-BP (either criterion)	Bone marrow	≥20% blasts
	Peripheral blood	≥20% blasts that last for at least 2 wk

MPN-blast phase

PV can transform to MPN-BP, often through an MF phase or, rarely, directly from the polycythemic phase. Transformation is defined as >20% blasts in the marrow or blood (Table 17-6). MPN-BP occurs in roughly 1% to 3% of patients treated with phlebotomy alone. In contrast, certain therapies such as Phosphorus-32 (^{32}P) treatment, chlorambucil, possibly busulfan, and alkylating agent combinations have been associated with increased risk of transformation to MPN-BP (up to 15-fold increased risk in randomized Polycythemia Vera Study Group [PVSG] trials). The ECLAP study noted a higher rate of AML/MDS transformation with pipobroman use. This agent is no longer available in the United States but is still available for use in Europe and elsewhere. Although early observational studies suggested that MPN-BP might be increased in patients receiving hydroxyurea (HU), the ECLAP study, the largest prospective PV study to date, enrolled 1638 patients and noted no increase in MPN-BP in patients treated with HU, with a median follow-up time of 8.4 years after PV diagnosis and 2.5 years after study enrollment. Other current therapies, including interferon alpha (IFN)α, anagrelide, and JAK inhibitors, do not increase the risk of leukemic transformation. Finally, certain acquired somatic mutations, including *ASXL1*, *IDH1/2*, and *SRSF2,* may increase risk.

Prognosis

PV is a chronic disease that is incurable without stem cell transplant; however, transplant is almost never done in the PV phase. In the contemporary era, age at diagnosis, leukocyte count at diagnosis, and thrombosis history influence prognosis. The life expectancy is between ~11 and 28 years depending on risk grouping (Table 17-7). Similar to MF and AML, additional somatic mutations in PV may further influence risk (*ASXL1*, *IDH1/2*, and *SRSF2*).

Management

The goals of therapy in PV include providing symptom relief, improving quality of life, and reducing risk for incident/recurrent thrombosis (and hemorrhage). Unfortunately, currently available therapies are not effective in preventing or delaying transformation. Management has been historically guided by vascular risk, but it is important to incorporate symptom burden into treatment decisions as well (Figure 17-2).

Hematocrit control

Therapeutic phlebotomy is a mainstay of current treatment. The target goal for phlebotomy was evaluated

Table 17-7 PV survival, based on risk factors

Age, y	>67 (5 points)
	57-66 (2 points)
	<57 (0 points)
Leukocytes	>15 × 10^9/L (1 point) vs <15 × 10^9/L
Prior thrombosis	Yes (1 point) vs No (0 points)
Risk group point cutoffs/survival	Sum above points. Median survival:
	Low-risk (0 points): 27.8 y
	Intermediate risk (1 to 2 points): 18.9 y
	High-risk (≥3 points): 10.9 y

Adapted from Tefferi A et al, *Leukemia*. 2013;27:1874-1881.

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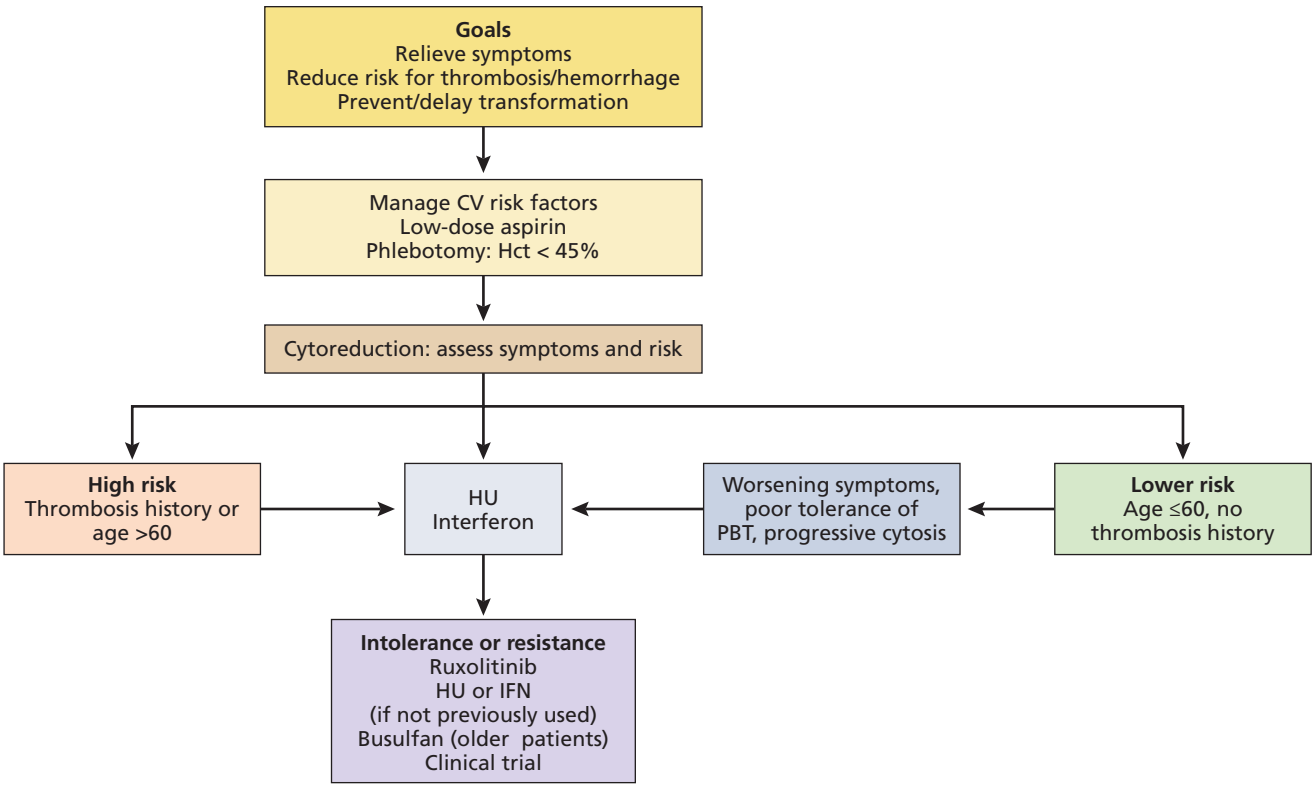

Figure 17-2 PV management algorithm. PBT, phlebotomy.

by the CYTO-PV study, in which patients were randomized to either strict hematocrit control (goal ≤45%) or less strict hematocrit control (goal 45%-50%). Therapeutic phlebotomy and/or cytoreductive therapies were used, per physician preference, to meet these goals. In those with a stricter hematocrit target <45%, there was a nearly 4-fold reduction in risk of cardiovascular (CV) death and major thrombosis. This study had a significant impact on practice, and a hematocrit of 45% or less is now the standard recommended goal for patients with PV. While it is not data-driven, many use a hematocrit of 42% or less as a target hematocrit in women. Phlebotomy to the point of iron deficiency may be associated with reactive thrombocytosis, but the thrombohemorrhagic risk in this clinical setting has not been delineated. Unless a patient is overtly symptomatic from the iron deficiency, iron supplementation should be avoided to prevent undue elevation in hematocrit levels.

Antiplatelet therapy

The ECLAP study, a double-blind randomized trial, compared low-dose aspirin with placebo among 518 patients who had no indication for anticoagulation and no preexisting clear indication or contraindication to aspirin therapy. The study demonstrated that low-dose aspirin (ie, 100 mg/d or less) reduces the rate of thrombosis and cardiovascular deaths in those receiving standard phlebotomy and supportive care. The aspirin-treated group experienced 60% fewer major thromboses and cardiovascular deaths (3.2% versus 7.9% absolute incidence) after roughly 3 years of follow-up. The ECLAP trial observed only a modest increase in epistaxis and no increase in major bleeding on low-dose aspirin. Low-dose aspirin also can effectively control erythromelalgia, aquagenic pruritus, and other vasomotor symptoms in many patients. Prior PVSG trials showed that higher doses of aspirin (ie, 500-900 mg/d) offer no added benefit but increased the risk of bleeding complications, especially when combined with dipyridamole. The role of clopidogrel and other antiplatelets or dosage regimens is not well defined.

Cytoreduction

Cytoreduction is typically reserved for high-vascular-risk patients, defined as those aged ≥60 years and/or with a

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thrombosis history. Additional indications include poor tolerance of phlebotomy, symptomatic thrombocytosis, progressive leukocytosis, symptomatic splenomegaly, and uncontrolled symptoms impacting quality of life.

Hydroxyurea

HU, a ribonucleotide reductase inhibitor, is most commonly-used for those requiring cytoreductive therapy. HU emerged as the cytoreductive agent of choice based on historical PVSG studies, showing a lower rate of thrombosis compared with phlebotomy alone and lower risks of secondary leukemia compared with chlorambucil and ^{32}P. The mutagenic and leukemogenic potential of HU has been a subject of concern; however, overall, the AML/MDS risk with chronic HU therapy appears lower in magnitude than with other cytoreductive agents, such as chlorambucil, ^{32}P, pipobroman, and busulfan. Nevertheless, because of uncertainty regarding these concerns, HU often is avoided in younger adults and should be used only after a thorough discussion of the potential risks and benefits. Additional adverse effects of HU include cytopenias, gastrointestinal (GI) disturbances, and, less commonly, chronic mucocutaneous ulcers. The prevalence of HU intolerance (hematological or nonhematological) or resistance (uncontrolled Hct, leukocytes, platelets, or spleen size) despite a sufficient dose/duration is ~10% to 20%. Whether or not an active phlebotomy requirement despite HU treatment increases thrombosis risk remains to be seen. Among the factors defining intolerance, the development of cytopenias on HU (intolerance) may have the most negative influence on prognosis. Intolerance or resistance is an indication to move on to second-line therapy. Importantly, HU is a teratogenic agent and should be avoided in those who might become pregnant (see "Pregnancy" section).

Interferons

Clinical practice guidelines recommend interferons as one potential frontline option in those who require cytoreduction, particularly for younger patients. Both short-acting and longer-acting IFNs have consistently demonstrated a capacity to control erythrocytosis, leukocytosis, and/or thrombocytosis. Adverse events, including fatigue, myalgias/influenza-like symptoms, mood change (in most extreme cases, suicidality), optic changes, emergence of autoimmunity, and neuropathy, have tempered enthusiasm. Recent studies with pegylated IFNα have demonstrated significant clinical efficacy, including clinical and molecular remissions in a substantial proportion of patients with improved tolerability; however, adverse events (AEs) are still limiting. Current trials are aimed at assessing the efficacy and safety of pegylated IFNα in a larger cohort of PV patients, either when compared directly with HU or when used as salvage following HU. Although these studies are ongoing and longer follow-up is needed, these agents currently appear noninferior when compared with HU. IFNα therapy is safe during pregnancy, in contrast to HU, which may be teratogenic. Another interferon preparation, known as ropeginterferon alfa-2b, has a longer half-life and every-2-week dosage. Ropeginterferon alfa-2b has been approved in Europe for use in PV, but it is not yet available in the United States.

JAK inhibition

Ruxolitinib is available for second-line use in the setting of an inadequate response to HU. The RESPONSE trial evaluated ruxolitinib versus best available therapy (BAT) in a cohort of PV patients with HU intolerance/resistance, active phlebotomy needs, and splenomegaly. Ruxolitinib-treated patients were more likely to meet the primary endpoint comprised of spleen volume reduction and hematocrit control when compared with those treated with BAT. There was also greater improvement in PV-related symptoms and a trend for a reduced number of thrombotic events in the ruxolitinib arm; however, this was neither a primary endpoint, nor was the study powered to detect differences between treatment groups. Longer-term follow-up shows durability in primary responders. A second phase 3 study, with similar patients (lacking splenomegaly), also showed superior hematocrit control in ruxolitinib-treated patients when compared with BAT (RESPONSE-2). Myelosuppression is less common in PV compared with MF, but AEs include weight gain, increase in cholesterol, increase in skin cancer in at-risk patients, and increase in infections such as zoster. Ruxolitinib may be particularly effective for control of pruritus.

Additional therapeutic considerations

Thrombotic events are treated with therapeutic anticoagulation in a similar manner to other patients who present with acute thrombosis. Blood count control, including phlebotomy to normalize the hematocrit, should be initiated if patients have a hematocrit >45%. The utility of platelet-pheresis for thrombocythemic patients with acute thrombosis, and the optimal target platelet count after depletion, is unknown. Antiplatelet therapy in addition to warfarin may be useful in selected cases of PV-associated arterial thrombosis, but only after the acute event is stabilized with full anticoagulation, and only if the potential

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additive risk of bleeding is considered acceptable. The optimal duration of anticoagulation continues to be unclear.

Abdominal vein thrombosis, including Budd-Chiari syndrome, portal vein occlusion, and mesenteric vein thrombosis, are all more frequently encountered in patients with MPNs. Of the MPN subtypes, these events may be most commonly observed in PV. In some cases, an MPN is entirely latent. The natural history of individuals who do not meet the WHO diagnostic criteria for MPNs but present an abdominal vein thrombosis and whose driver mutation remains unclear. In general, indefinite anticoagulation is recommended for these patients, and cytoreduction is indicated if cytosis is present. Because these patients may have complications from portal hypertension (HTN), cotreatment with hepatology is often needed, especially in those with esophageal varices.

The PV-symptom burden can be considerable, even in traditionally lower-risk patients (Table 17-6). Low-risk, but symptomatic, patients may require therapy beyond phlebotomy and aspirin. Problematic symptoms can include fatigue, pruritus, and symptoms from splenomegaly. Pruritus may be a particularly disturbing symptom that often is unresponsive to phlebotomy or cytoreductive therapy. JAK inhibition with ruxolitinib has been helpful for some patients. Additionally, antihistamines, psoralen and UV-A phototherapy, cholestyramine, or selective serotonin reuptake inhibitors (ie, paroxetine) may provide symptomatic relief. Cytoreductive therapy with HU or IFN (IFNα or pegylated IFNα) may help in refractory cases. Painful splenomegaly and unacceptable hypercatabolic symptoms usually require treatment with HU or IFN (IFNα or pegylated IFNα).

Patients with PV (as well as ET or MF) undergoing elective surgical procedures may have an increased risk of bleeding and/or thrombosis, even despite appropriate blood count control and prophylactic measures. Emergency surgical procedures should proceed as necessary but with awareness of a higher risk of vascular complications, particularly in those with uncontrolled thrombocytosis, erythrocytosis, or leukocytosis. Preparation for elective procedures includes hematocrit control for those with PV and, quite possibly, cytoreduction to control leukocytosis/thrombocytosis, depending on the nature of the procedure. Hematologists should discuss whether antiplatelets should be held prior to the surgery. Provided no contraindications, ideally, patients are treated with venous thromboembolism (VTE) prophylaxis after surgery. Hematologists and the surgeon can decide on the timing of reinitiation of antiplatelet therapy.

KEY POINTS

- PV is a clonal disorder associated with *JAK2* V617F or *JAK2* exon-12 mutations.
- PV must be differentiated from relative/secondary causes of erythrocytosis.
- PV patients may exhibit a range of symptoms that can be related to inflammatory cytokines, vascular phenomena, or disease progression.
- Thrombosis is the major cause of morbidity and mortality in the first decade of the disease, while progression to post-PV MF or MPN-BP becomes a concern in the second decade.
- Cornerstones of PV management include CV risk factor modification, low-dose aspirin, and phlebotomy for a Hct target of 45% or less.
- Cytoreductive therapy (HU or pegylated IFN) is indicated in patients with high thrombosis risk (age ≥60 or prior thrombosis) or those with bothersome symptoms.
- Ruxolitinib is approved as second-line therapy for patients whose PV is resistant or intolerant to HU.

Essential thrombocythemia

CLINICAL CASE

A 40-year-old previously healthy landscaper complained of increased fatigue and migraines. A CBC revealed a platelet count of 1062×10^9/L. She was then referred to a hematologist, whose evaluation included iron studies and inflammatory markers that were within normal limits. Fluorescence in situ hybridization (FISH) for *BCR-ABL1* and *JAK2* V617F testing were negative, but she did have a calreticulin mutation. Her bone marrow was slightly hypercellular with mature megakaryocytic hyperplasia and no reticulin fibrosis.

Introduction

ET is about as prevalent as PV, with ~150,000 cases in the United States (estimated from claims databases) and an annual incidence rate of ~0.5 to 1.5 cases per 100,000 persons per year. The median age at diagnosis is approximately in the mid-seventies; however, the distribution of cases is quite broad. There is a predominance of women with ET compared with men. Morbidity and mortality from ET in the first decade of the disease are predominantly related to thrombotic, vasomotor, and, less common hemorrhagic complications. Longstanding ET, like PV, can progress to post-ET MF or transform to MPN-blast phase.

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Diagnosis

Thrombocytosis can either be primary (ie, owing to an MPN such as ET) or secondary (reactive). Secondary causes of thrombocytosis are much more common and include iron deficiency; infection; inflammation; surgery, especially the postsplenectomy state; trauma; tissue injury or infarction; and malignancy. Although reactive conditions infrequently cause elevations in platelet counts of >2000 × 10^9/L, the absolute value of the platelet count usually does not distinguish reactive thrombocytosis from ET. It is also important to exclude other MPNs, which can all present with thrombocytosis (especially "occult" PV, PMF, and CML) and MDS (especially 5q– syndrome, chromosome 3(q21;q26) abnormalities, or MDS/MPN with ring sideroblasts and thrombocytosis [MDS/MPN-RS-T, formerly RARS-T]). Hereditary/familial thrombocytosis is also in the differential diagnosis. As noted, germline *MPL* and *JAK2* mutations have been described in hereditary thrombocytosis and in those initially suspected to have "triple-negative" ET.

Diagnostic criteria for ET

Diagnostic criteria for ET take incorporate thrombocytosis (sustained platelet count ≥450 × 10^9/L), characteristic bone marrow morphologic features, presence of typical "driver" mutations or another clonal marker, and exclusion of other entities (Table 17-8). Importantly, exclusion of PV is necessary to diagnose ET. In other words, an evaluation for PV supersedes an evaluation for ET in patients with both polycythemia and thrombocytosis, both of which commonly co-occur. The WHO revised the diagnostic criteria for ET in 2016. The most important difference is the inclusion of *CALR* mutations as a representative clonal marker. As discussed in the MF section, it is important to distinguish ET from prefibrotic/early MF, given the prognostic implications.

Table 17-8 WHO 2016 diagnostic criteria for ET

Major	1. Sustained platelet count ≥450 × 10^9/L
	2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with mature megakaryocytes, with hyperlobulated nuclei; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis and very rarely grade 1 increase in reticulin
	3. Not meeting WHO criteria for PV, PMF, CML, MDS, or another myeloid neoplasm
	4. Presence of *JAK2*V617F, *CALR*, or *MPL* mutation
Minor	Presence of a clonal marker or exclusion of reactive thrombocytosis
Diagnosis	All 4 major criteria, or the first 3 major criteria and minor criteria

Adapted from Arber DA et al, *Blood*. 2016;127(20):2391-2405.

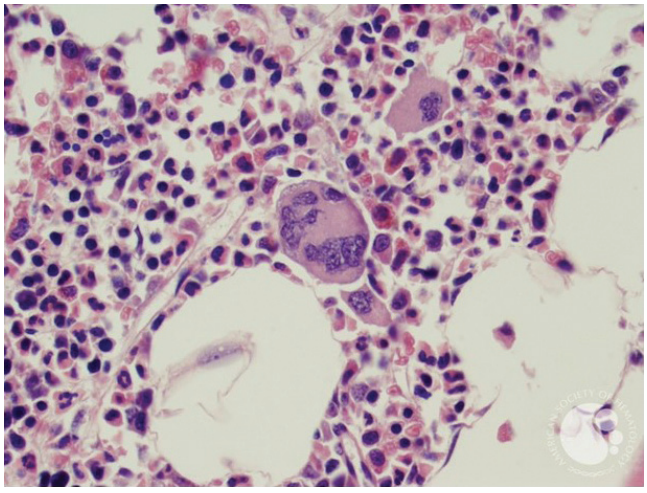
Blood and bone marrow findings

Anemia and leukocytosis are less common in ET, and the presence of these, along with increased LDH, should raise suspicion for prefibrotic/early MF. The peripheral blood smear often is notable for large or giant platelets with occasional eosinophils, basophils, or circulating megakaryocyte fragments. Bone marrow evaluation is important in suspected ET cases to assess for characteristic histopathologic features, and rule out other myeloid disorders such as MF or MDS/MPN-RS-T. Increased numbers and clusters of large megakaryocytes with hyperploid nuclei are seen in most marrow samples, and the bone marrow may be normocellular or only mildly hypercellular (Figure 17-3). Megakaryocyte atypia and hypercellularity/left-shifted granulopoiesis should not be seen. Significant reticulin and collagen fibrosis are minimal or absent. If >15% ring sideroblasts are present, MDS/MPN-RS-T rather than ET must be considered.

Disease course and prognosis

The disease course of ET can range from a near-normal life expectancy to significant morbidity, mortality, and death from vascular events or progressive disease. A common misperception is that ET patients are asymptomatic—recent studies demonstrate that patients with ET, although generally less symptomatic than those with PV or MF, can have significant vascular, vasomotor, and cytokine-related symptoms that impact quality of life.

Figure 17-3 ET bone marrow. The marrow is hypercellular for age with increased megakaryocytes. The megakaryocytes are dispersed throughout the marrow and include frequent large forms with abundant cytoplasm and deeply lobated nuclei. Source: ASH Image Bank/Elizabeth L. Courville.



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Vascular events in ET

Up to 30% of ET patients have had a thrombotic event prior to or around the time of their MPN diagnosis. In a population-based study, the hazard ratio for overall thrombosis was 3.5, 2.2, and 1.7 at 3 months, 1 year, and 5 years from diagnosis, compared to controls. Like PV, older age and prior thrombosis history influence risk, as do cardiovascular risk factors (including smoking, hypertension, diabetes, and dyslipidemia). The driver mutational profile is also important because lower rates of thrombosis have been observed in patients with *CALR* mutations when compared with those with *JAK2* mutations. Several risk assessment tools exist to help predict the likelihood of thrombosis in patients with ET. A commonly-used tool, the revised IPSET-thrombosis score, stratifies patients into 4 risk groups using age, history of prior thrombosis, and *JAK2* mutation status (Table 17-9). Similar to PV, leukocytosis is likely to increase thrombosis risk. Current data does not suggest that the absolute platelet number predicts thrombosis risk; rather, studies have found a correlation between bleeding risk and extreme thrombocytosis, especially when $>1500 \times 10^9$/L. This risk is owing to development of acquired von Willebrand disease.

Disease progression

Post-ET myelofibrosis

Like PV, progression to MF is suspected in the presence of changing symptoms, new or progressing splenomegaly, development of anemia, and increased LDH, along with blood smear, bone marrow changes, and progression of fibrosis (Table 17-6). The risk of progression in WHO-defined ET nears 10% at 15 years. In those with a more rapid progression, it is possible that the original diagnosis was early/prefibrotic MF. Apart from disease duration, other risk factors for progression to post-ET MF include leukocytosis, anemia, and advanced age. With regards to mutational status, it is possible that MF progression rates are increased in those with *CALR* mutations. Furthermore, mutations in *SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, or *EZH2* are considered adverse variants that may impact ET progression to MF.

MPN-blast phase

Diagnostic criteria for MPN-BP from ET are also shown in Table 17-6. In the absence of leukemogenic therapy (radiophosphorus, alkylators), progression to MPN-BP directly from ET, without an intervening post-ET MF phase, is uncommon (~2% at 15 years). As indicated previously, adverse variants identified in ET (*SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, or *EZH2*) may impact risk for leukemic transformation.

Survival

In a study of 800 WHO-defined ET patients, multivariate analysis found age, leukocytosis, and prior vascular events as most prognostic for survival (Table 17-10). Although inferior to age/sex-matched controls, another large study suggested a median life expectancy of near 20 years. Driver mutational status did not impact survival in this study. In keeping with potential influence on MPN-BP and post-ET MF transformation, adverse variants impacted survival compared with those without such mutations.

Management

Goals of therapy in ET also include providing symptom relief, reducing risk for incident/recurrent thrombosis (and hemorrhage), and preventing transformation. Similar to PV, the latter goal is not yet achievable with current medical therapy. Although management is strongly influenced by vascular risk assessment, it is important to also incorporate symptom assessment into therapeutic planning (Figure 17-4).

Antiplatelet therapy

Unlike PV-related studies, there are no randomized studies supporting use of aspirin in ET patients. A meta-analysis suggested inconsistent evidence and an uncertain benefit-risk ratio. Rather, aspirin use in ET is selective and certainly considered in the presence of CV risk factors. Additionally, vasomotor symptoms and erythromelalgia are often responsive to therapy with aspirin. Mutational status may influence decision making. A retrospective study

Table 17-9 Revised IPSET-thrombocytosis

Category	Age (y)	Thrombosis history	*JAK2* status	Yearly thrombosis risk
Very low risk	≤60	None	Negative	~0.4%-0.6%
Low risk	≤60	None	Positive	~0.8%-1.6%
Intermediate risk	>60	None	Negative	~1.4%-1.6%
High risk*	>60	Positive	Positive	~2.5%-4%

Adapted from Gerds AT, Mesa R, *The Hematologist*. 2017;14(6) (https://doi.org/10.1182/hem.V14.6.7895).

*High-risk patients are either older than 60 with *JAK2* mutations or any patient with a prior thrombotic event.

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Table 17-10 ET survival in WHO-defined ET (3 groups)

Parameter	0 points	1 point	2 points
Age, y	<60	—	≥60
Leukocytes ($\times 10^9$/L)	<11	≥11	—
History of thrombosis	No	Yes	
Low risk	0 points:	Median survival not reached (>30 y)	
	1-2 points:	Median survival: 24.5 y	
	3-4 points:	Median survival: 13.8 y	

Adapted from Passamonti F et al, *Blood*. 2012;120(6):1197-1201.

suggested that patients with *CALR*-mutant ET did not have reduction in thrombosis risk but may have a possible increase in bleeding risk. In those with extreme thrombocytosis, excluding acquired von Willebrand disease is important prior to a recommendation of aspirin. Like PV, the role of clopidogrel or other antiplatelet agents in ET is unknown. Whether aspirin is necessary in asymptomatic low-risk patients with ET is unknown and remains a point of clinical judgment. Alternative aspirin regimens (ie, 81 mg twice a day orally) are under investigation.

Cytoreduction

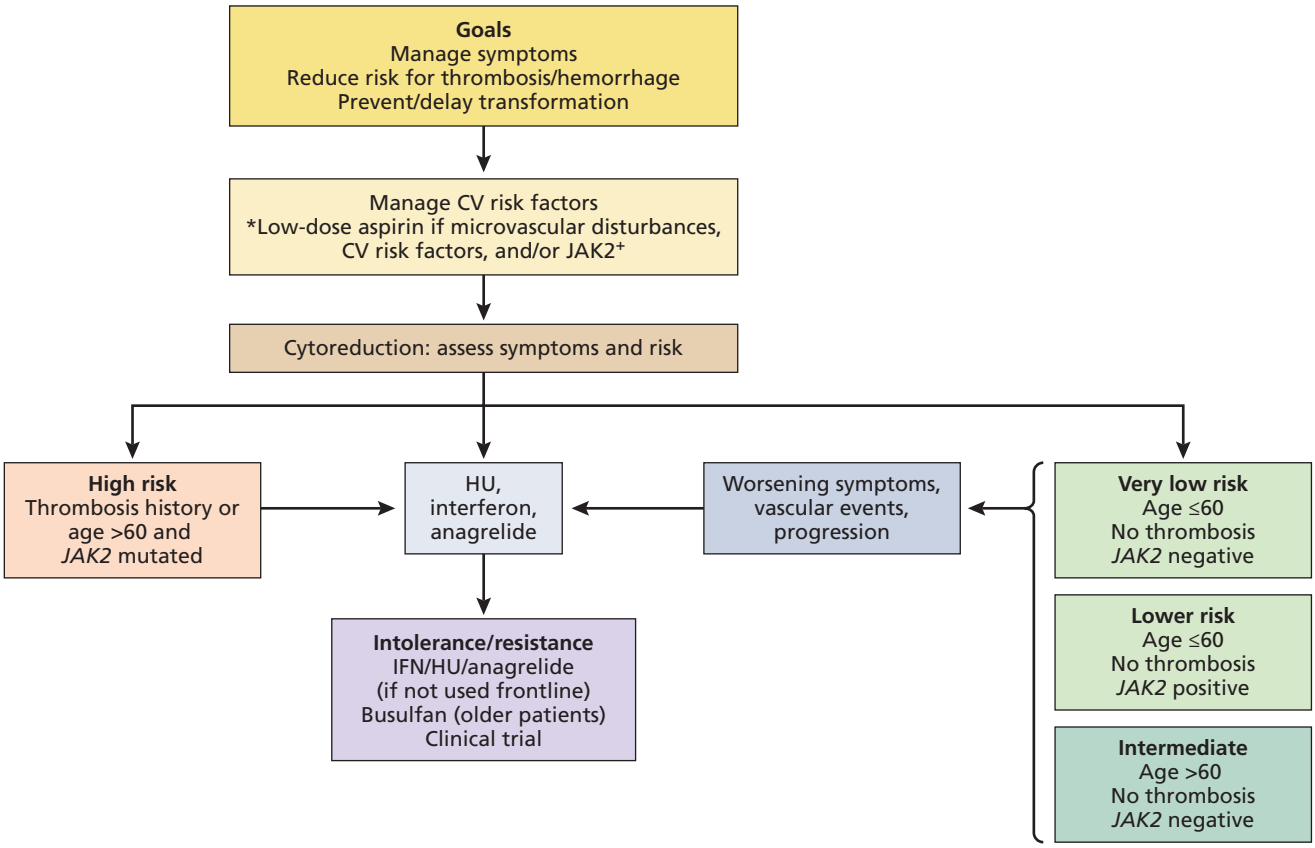
Cytoreduction is considered in those who are high-risk by IPSET-thrombosis score or have problematic ET-related symptoms. Options for cytoreduction include HU, interferons, and anagrelide.

Hydroxyurea

The first randomized trial of 114 patients of HU versus placebo demonstrated a decrease in thromboembolic events in high-risk ET patients treated with HU. A follow-up report of this study (median treatment time, 73 months) revealed a continued benefit for HU: 45% of patients in the control group experienced a thrombotic event versus 9% of patients in the HU group. Of note are 1.7% of control patients and 3.9% of the group receiving HU who developed secondary myeloid malignancies (AML/MDS), a difference that was not statistically significant.

A second important randomized study (PT-1 trial) included 809 high-risk ET patients treated with aspirin and randomized to either HU or anagrelide with a goal platelet count of $<400 \times 10^9$/L. After a median follow-up of 39 months, compared with HU plus aspirin, patients receiving anagrelide plus aspirin had increased rates of

Figure 17-4 ET management algorithm.



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arterial thrombosis (but a lower rate of venous thrombosis), serious hemorrhage, and development of marrow fibrosis, despite similar platelet count control. Patients receiving anagrelide were more likely to withdraw from their assigned treatment because of toxicity or treatment failure. Taken together, these studies supported HU as a frontline cytoreductive in high-risk patients. In those without high-risk features, a randomized controlled study showed no benefit to adding hydroxyurea to an aspirin regimen.

Anagrelide

A subsequent study compared anagrelide to HU in those with WHO-defined ET (ANAHYDRET). This noninferiority study (excluding aspirin in the anagrelide arm with concerns of intensifying the antiplatelet properties of anagrelide) demonstrated no significant difference between HU and anagrelide with regard to rate of major/minor thrombosis, hemorrhage, or discontinuation rates. It has been suggested that use of WHO-ET criteria over PVSG criteria (which may have included patients with leukocytosis, a risk factor for thrombosis), inclusion of newly-diagnosed or untreated patients, and restriction of aspirin use may have accounted for differences in study outcomes when comparing ANAHYDRET to PT-1. Practice patterns and guidelines vary on which agent to use first, with anagrelide as a potential frontline therapy per National Comprehensive Cancer Network (NCCN) and second-line therapy per European Leukemia Net (ELN).

Interferons

Both short-acting and longer-acting IFNs have demonstrated efficacy in ET and are considered frontline options. Recent studies with pegylated IFNα have demonstrated significant clinical efficacy, including hematological and molecular responses (in both *JAK2* and *CALR*-mutant ET) in a substantial proportion of patients. These experiences have been reported in previously treated ET patients in clinical trial and real-world settings. Ongoing trials are aimed at assessing the efficacy and safety of pegylated IFNα in newly-diagnosed, high-risk ET, compared with HU. A second ongoing phase 2 study evaluates salvage use of pegylated-interferon in those with prior HU resistance or intolerance. Additional studies of ropeginterferon versus anagrelide in ET are also underway. IFNα therapy is considered reasonably safe during pregnancy, in contrast to HU and anagrelide, which may be teratogenic (discussed further in the following).

JAK inhibition

The JAK1/2 inhibitor ruxolitinib was studied in a nonrandomized phase 2 study of patients with ET after HU failure and led to improvements in thrombocytosis, ET-related symptoms, and splenomegaly. However, a subsequent randomized phase 2 study (MAJIC-ET), comparing ruxolitinib to best available therapy in those with HU resistance or intolerance, did not demonstrate any significant differences in complete response, thrombosis, hemorrhage, or transformation rates. Some symptoms, like pruritus, were improved in those treated with ruxolitinib. Anemia and infections were more common in those treated with ruxolitinib. Based on this study, ruxolitinib is not yet recommended for use in ET.

Additional therapeutic considerations

As is the case with PV, acute management of vascular events is heterogeneous. Historically, in the setting of acute arterial or venous events, emergency platelet-pheresis was a consideration to reduce the platelet count if extremely high; however, this is not a data-driven practice. Anticoagulation is indicated for those with venous events, but the type of anticoagulant and duration is still unclear. Indefinite anticoagulation is typically reserved for patients with abdominal vein thrombosis or recurrent thromboses. In either circumstance, the patient should be monitored closely for bleeding while receiving anticoagulation. Like PV, while treatment is guided by vascular risk, lower-risk patients with uncontrolled symptoms may be candidates for cytoreduction.

Pregnancy

MPNs may increase the risk of miscarriage, abruptio placentae, preeclampsia, intrauterine growth retardation, and maternal VTE and/or hemorrhage. Based on the age distribution of MPN patients, the pregnancy literature primarily includes women with ET, as compared with PV and MF. Consensus guidelines advise on management strategies, but none of the strategies are proven to improve outcomes. In low-risk pregnancies, it is recommended to control the hematocrit in patients with either preexisting PV to <45% or a midgestation-specific range, whichever is lower. Aspirin is recommended during the antepartum, and prophylactic low-dose molecular-weight heparin may be recommended in the postpartum period. High-risk pregnancies are defined by prior thrombosis or hemorrhage attributed to MPN, previous pregnancy complications, or extreme thrombocytosis (>1500 × 10^9/L). High-risk patients may require low-molecular-weight heparin throughout pregnancy, while monitoring for bleeding complications. If there has been previous major bleeding, avoidance of aspirin may be necessary. If the platelet count is >1500 × 10^9/L, interferon therapy may be required. Similarly, in those on preexisting cytoreductive therapy, only IFNα is felt to be safe during pregnancy. No drug is

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actually approved or licensed for use during pregnancy, but the risk profile in high-risk patients is typically felt to be acceptable with the use of IFNα; whereas, HU, anagrelide, and ruxolitinib are either known or suspected teratogens.

KEY POINTS

- A diagnosis of ET requires exclusion of reactive causes, as well as other myeloid neoplasm mimics.
- *JAK2*, *CALR*, or *MPL* mutations are present in 80% to 90% of ET patients; their presence proves the existence of a clonal myeloid disorder, but these mutations are not specific for ET and their absence does not exclude a diagnosis of ET.
- Vascular risk classification is based on age, thrombosis history, and mutational status.
- Life expectancy is longer compared with those with other MPNs, but patients are at-risk for ET-related morbidity and mortality over time because of constitutional symptoms, vascular disturbance, and disease progression or transformation.
- Antiplatelet therapy is used selectively in ET; cytoreductive agents such as HU, IFN, or anagrelide are options for higher-risk patients or those with uncontrolled symptoms.

Myelofibrosis (prefibrotic MF, overt primary MF, and post-ET/PV MF)

CLINICAL CASE

A 71-year-old man with a history of prostate cancer, status post prostatectomy, gout, and cholecystitis presented with early satiety, left upper quadrant pain, and night sweats. Physical examination revealed an enlarged spleen (spleen edge palpated 15 cm below the left subcostal margin at the midclavicular line). Leukocytosis (WBCs = 21×10^9/L), normocytic anemia (Hgb = 9.4 g/dL), and a normal platelet count (292×10^9/L) were noted. Review of the peripheral blood smear revealed circulating blasts, teardrop cells, nucleated red blood cells, and immature WBCs (myelocytes and metamyelocytes). A bone marrow biopsy specimen revealed a hypercellular marrow with megakaryocytic hyperplasia and atypia, marrow blasts of 4%, and grade MF-2 reticulin fibrosis. *JAK2* V617F was detected with an allele burden of 34%. Metaphase cytogenetics showed 46,XY,del(13q) in all 20 metaphases examined. An *ASXL1* mutation was also noted.

Introduction

The term "myelofibrosis" encompasses several disease subtypes: prefibrotic MF, overt primary MF, and MF that evolved from ET or PV (post-ET MF and post-PV MF). The annual incidence of MF has been reported at between 0.2 to 0.5 cases per 100,000 persons per year. The median age at diagnosis of PMF is ~65 years, with 70% of patients diagnosed after 60 years of age and approximately 10% of patients diagnosed at <45 years of age. The natural history of MF is quite variable depending on the presence or absence of poor prognostic features. The clinical features are also quite heterogeneous, and often include cytopenias (as opposed to ET/PV where cytoses are expected), constitutional symptoms, and/or hepatosplenomegaly. Management is both risk-stratified (with higher risk, eligible patients considering stem cell transplant) and symptom-guided to achieve the goals of improving both length and quality of life.

Diagnostic criteria

The diagnosis of MF requires attention to bone marrow morphologic features, cytogenetic or molecular abnormalities, laboratory parameters, and clinical findings (spleen size). The 2016 WHO revisions to MF diagnostic criteria included explicit distinctions between prefibrotic MF and overt MF (Tables 17-11 and 17-12). Compared with prefibrotic MF, overt MF has more extensive reticulin fibrosis and, often, leukoerythroblastosis. In both cases, a driver mutation is identified in nearly 90% of patients. When results are negative, other clonal markers may be identified, satisfying this criterion. Prefibrotic MF can be difficult to distinguish from ET; however, marrow morphologic features (ie, megakaryocyte atypia) and minor clinical criteria should be helpful in distinguishing these 2 entities. Diagnostic criteria for post-ET MF and post-PV MF appear in Table 17-6.

It is important to note that the identification of fibrosis in the bone marrow does not necessarily make the diagnosis of "myelofibrosis." There are many other disease states that lead to marrow fibrosis. The differential diagnosis for marrow fibrosis should include other bone marrow malignancies (ie, MDS with fibrosis, acute leukemias, lymphomas, CML, or multiple myeloma), metastatic carcinoma to the marrow, infections (ie, tuberculosis, some viral or fungal infections), and autoimmune disease. A comprehensive list of the other malignant and nonmalignant causes of marrow fibrosis are listed in Table 17-13.

Blood and bone marrow features

Similar to patients with ET and PV, patients with MF can have elevated blood cell counts, namely leukocytosis and thrombocytosis. Unlike ET and PV, patients with

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Table 17-11 Diagnostic criteria for prefibrotic PMF

	Criteria
Major	1. Megakaryocyte proliferation and atypia, without reticulin fibrosis >grade 1, with increased age-adjusted cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting WHO criteria for CML, PV, ET, MDS, or other myeloid neoplasm 3. Presence of a clonal marker, such as *JAK2*, *CALR*, or *MPL* mutations; in the absence, presence of another marker (*ASXL1*, *EZH2*, *TET2*, *IDH*, *SRSF2*, *SF3B1*), or absence of reactive causes of bone marrow fibrosis
Minor	1. Anemia 2. Leukocytes ≥11 × 10^9/L 3. Palpable splenomegaly 4. LDH above reference range
Diagnosis	Diagnosis requires meeting all 3 major criteria and at least 1 minor criterion

Adapted from Arber DA et al, *Blood*. 2016;127(20):2391-2405.

Table 17-12 Diagnostic criteria for overt PMF

Disease	Criteria
Major	1. Megakaryocyte proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 2. Not meeting WHO criteria for PV, ET, CML, MDS, or another myeloid neoplasm 3. Presence of *JAK2*, *CALR*, or *MPL* mutations; in their absence, presence of another clonal marker (*ASXL1*, *EZH2*, *TET2*, *IDH*, *SRSF2*, *SF3B1)*; or absence of reactive fibrosis
Minor	1. Anemia 2. Leukocytes ≥11 × 10^9/L 3. Palpable splenomegaly 4. Increased LDH 5. Leukoerythroblastosis
Diagnosis	Diagnosis requires meeting all 3 major criteria and at least 1 minor criterion

Adapted from Arber DA et al, *Blood*. 2016;127(20):2391-2405.

Table 17-13 Differential diagnosis of MF

Acute panmyelosis with myelofibrosis
MDS with fibrosis
Late-stage PV, ET, or CML with evolution to myelofibrosis
Hairy cell leukemia
Hodgkin lymphoma
Non-Hodgkin lymphoma
Plasma cell dyscrasias
Acute lymphoblastic leukemia
Metastatic carcinoma
Multiple myeloma
Chronic myelomonocytic leukemia
Systemic mastocytosis
Eosinophilic leukemia
Granulomatous infections (tuberculosis, histoplasmosis)
Renal osteodystrophy
Autoimmune MF

MF can also have low blood cell counts, including any combination of anemia, thrombocytopenia, and/or leukopenia. Because of the high cell turnover, LDH, bilirubin, and uric acid levels are commonly increased. Haptoglobin levels may be decreased, and there may be other clinical and laboratory indicators of low-grade hemolysis. In both prefibrotic MF and overt MF, an increase in atypical megakaryocytes should be present in the marrow. These megakaryocytes often cluster (Figure 17-5) and may have hyperchromatic or irregularly folded nuclei. Progressive fibrosis is characterized by accumulation of extracellular reticulin fibers (revealed by silver staining) and collagen fibers (revealed by trichrome staining). In advanced stages of MF, the hematopoietic space may become completely replaced by fibroblasts and extracellular matrix material. Osteosclerosis may develop in some cases. With increasing degrees of fibrosis, a diagnostic marrow aspirate often is unobtainable, yielding a "dry tap."

Proliferation of fibroblasts and other mesenchymal cells that lead to bone marrow fibrosis has been linked to inflammatory response cytokines, megakaryocyte-derived, and monocyte-derived growth factors. Growth factors include platelet-derived growth factor (PDGF), basic fibroblast-growth factor, and transforming growth factor beta, which also contributes to the stromal reaction. Elevated levels of interleukin 1 (IL-1) and tumor necrosis factor alpha are associated with augmented production or release of PDGF, basic fibroblast-growth factor, and angiogenic factors such as vascular endothelial growth factor. Another unique feature of MF includes egress of circulating $CD34^+$ cells, which can be 50-fold higher than in PV or ET. Higher levels of circulating $CD34^+$ cells in MF are associated with more advanced bone marrow fibrosis. This egress partially explains the presence of EMH, which can be observed in the liver and spleen. The presence of EMH can also be observed very rarely in other sites such as the vertebral column, paraspinal or intraspinal lesions, which can lead to cord compression; lung, which can associate with pulmonary hypertension; pleura; retroperitoneum; eye; kidney; bladder; mesentery; and skin.

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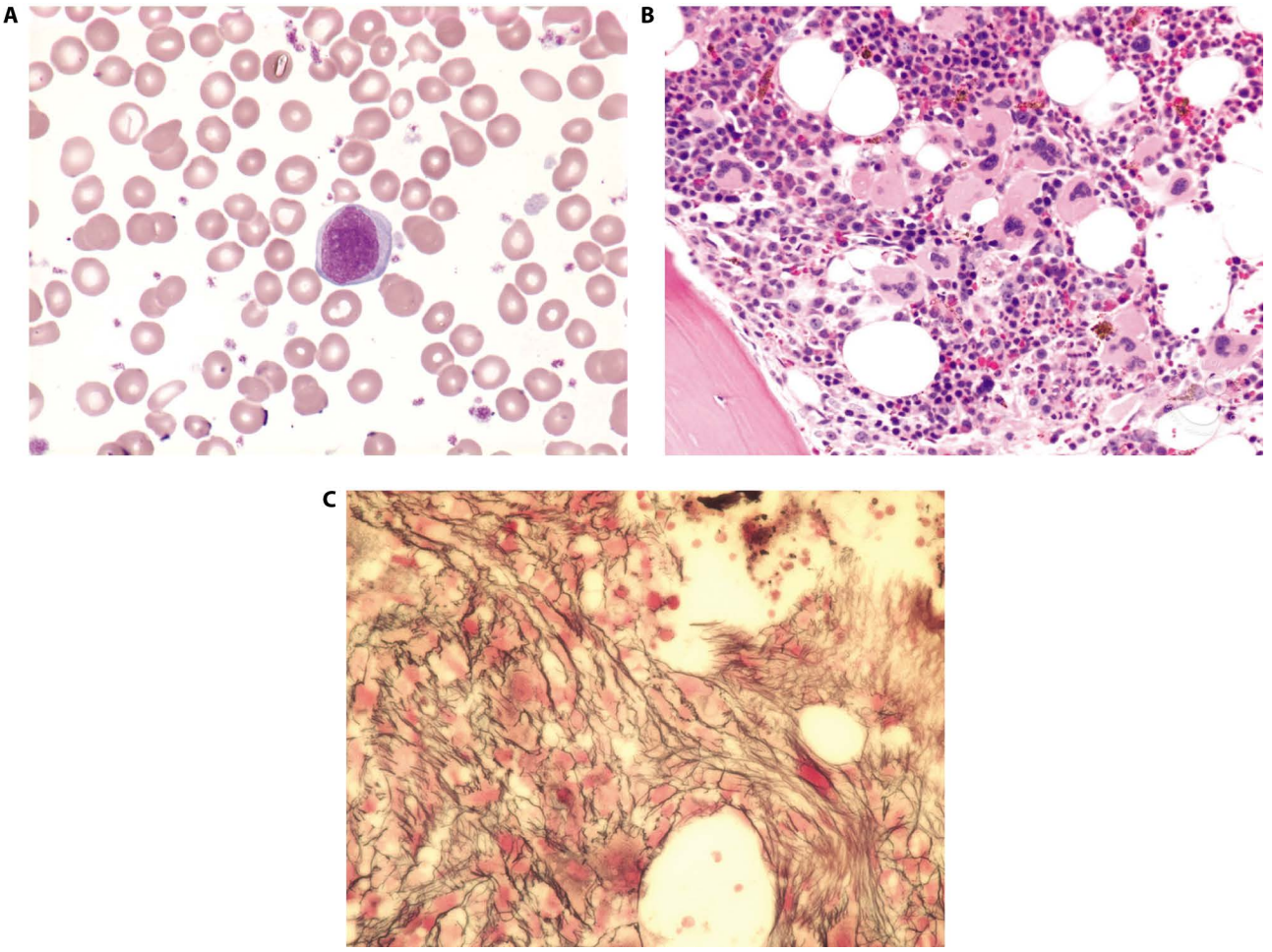

Figure 17-5 MF blood smear and bone marrow findings. (A) Blasts circulating in the peripheral blood can be found. (B) Megakaryocytic clustering is shown. The megakaryocytes are of variable size and show dysplastic nuclear changes. This finding was noted in a patient with a diagnosis primary myelofibrosis. (C) Marked reticulin fibrosis is demonstrated by a silver stain. Source: ASH Image Bank.

Disease course

In general, patients with MF tend to experience an increased symptom burden compared with those who have ET or PV. Such symptoms are often hypercatabolic and inflammatory in nature, and may include fever, night sweats, or weight loss. Fatigue is the most common and most severe symptom reported. Pruritus and bone and muscle pain also occur. Splenomegaly-associated symptoms are common, including pain/abdominal discomfort and early satiety. Portal hypertension with ascites can complicate the disease course and can arise from portal vein thrombosis, EMH in the liver, or increased blood volume in the setting of massive splenomegaly. As stated previously, rare consequences from nonhepatosplenic EMH may also develop. Pulmonary hypertension can occur and is often underrecognized. Anemia is also common. Nearly 75% patients will have a hemoglobin value less than normal, with ~50% having a hemoglobin value of <10 g/dL, and 25% being red cell transfusion dependent. Anemia is multifactorial and can result from ineffective erythropoiesis, inflammatory iron sequestration from elevated hepcidin, splenic sequestration, autoimmune hemolysis, myelosuppression from medication, or bleeding from portal HTN. Palliation of the major symptoms that impact quality of life is a major goal of MF-directed therapy.

Most patients die while the disease remains in the chronic MF phase; however, transformation to MPN-BP can occur and prove fatal in up to 30% of patients. Other causes of death stem from cardiovascular complications/thrombosis or bleeding, often in the setting of portal HTN. In the setting of an unrelated illness, bone marrow failure, infection, and deterioration, such as infection, might also be causes of death.

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Prognosis

Prognostic scoring systems for patients with MF are constantly evolving. Most leverage a combination of clinical and laboratory features, with newer models incorporating cytogenetic and molecular abnormalities. These prognostic models can help evaluate risk of transformation to MPN-BP and estimate survival. These evaluations can be clinically useful when discussing different therapeutic options with patients such as investigational agents, helping to direct goals of care conversations, and as one tool to help specify those in need of stem cell transplant consideration. Several of the prognostic scoring systems used most frequently in clinical care are summarized in Tables 17-14 and 17-15.

The presence of advanced age, constitutional symptoms, anemia (Hgb <10 g/dL), leukocytosis (>25 × 10^9/L), and circulating blasts (≥1%) were found to contribute to poor outcomes and became the basis for the development of the International Prognostic Scoring System (IPSS). This score was designed primarily to evaluate prognosis at the time of original diagnosis. The Dynamic International Prognostic Scoring System (DIPSS) accounts for acquisition of additional risk factors with time. The same factors were considered in both scoring systems, but hemoglobin <10 g/dL was given a higher score (2 points) compared with other risk factors in the IPSS. The next iteration, DIPSS-Plus, added transfusion dependence, thrombocytopenia (<100 × 10^9/L), and unfavorable karyotype to further refine prognosis.

In the molecular era, it has become clear that the type of driver mutation influences MF prognosis. First, prognosis is generally better in those with *CALR* mutations compared with other driver mutations, intermediate in those with *JAK2* or *MPL* mutations, and the most concerning in patients lacking any driver mutation ("triple-negative"). Even more nuanced, it has been suggested that the favorable prognosis associated with *CALR* mutations is restricted to those with type 1 mutations (52-bp deletions) or type-1 like based on modeling of the mutation. Moreover, studies have demonstrated a negative impact of high-molecular risk (HMR) mutations (*IDH1/2*, *EZH2*, *ASXL1*, and *SRSF2*) on leukemia-free and overall survival (OS), especially when more than 2 of these are present. Subsequent MF prognostic scoring system incorporates these molecular risk factors, along with clinical, laboratory, and histological features, in patients of a potential transplant age (Mutation and Karyotype-enhanced International Prognostic Scoring System, aka MIPSS70 and MIPSS70plus). Traditionally, these systems have been derived via the study of overt primary MF patients, but they have been used on those with post-ET and post-PV MF. Specific to those with post-ET and post-PV MF, the MYSEC-PM score takes age, constitutional symptoms, anemia, thrombocytopenia, and a *CALR*-unmutated status into account.

Management

The management of MF is influenced by disease risk and symptom burden. Disease risk classification is used to aid

Table 17-14 IPSS-derived prognostic scoring systems used in PMF

Risk factor	IPSS (no. of points)	DIPSS (no. of points)	DIPSS-Plus (no. of points)
Age >65 y	1	1	DIPSS low = 0
Constitutional symptoms★	1	1	DIPSS Int-1 = 1
Hgb <10 g/dL	1	2	DIPSS Int-2 = 2
WBC count >25 × 10^9/L	1	1	
Blood blasts ≥1%	1	1	DIPSS-high = 3
RBC transfusion dependence	–		1
Thrombocytopenia (<100 × 10^9/L)	–		1
Unfavorable karyotype†	–		1
Risk group	**Points: median survival (y)**	**Points: median survival (y)**	**Points: median survival (y)**
Low	0: 11.3	0: NR	0: 15.4
Intermediate-1	1: 7.9	1-2: 14.2	1: 6.5
Intermediate-2	2: 4.4	3-4: 4	2-3: 2.9
High	≥3: 2.3	5-6: 1.5	4-6: 1.3

Data from Cervantes F et al, *Blood*. 2009;113:2895-2901; Passamonti F et al, *Blood*. 2010;115:1703-1708; and Gangat N et al, *J Clin Oncol*. 2011;29:392-397.

NR, not reached; RBC, red blood cell.

★Constitutional symptoms include fever, night sweats, weight loss >10% from baseline in the year prior to diagnosis.

†Unfavorable karyotype includes complex karyotype, 1 or 2 abnormalities that includes +8, −7/7q−, i(17q), −5/−5q, 12p−, inv(3), 11q23 rearrangement.

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Table 17-15 MIPSS70 scoring systems

Risk factor	MIPSS70 (no. of points)	MIPSS70plus (no. of points)	MYSEC-PM* (no. of points) (also includes age)
Constitutional symptoms	1	1	1
Hgb <10 g/dL	1	1	2 (Hgb <11 g/dL)
WBC count >25 × 10^9/L	2	—	—
Thrombocytopenia (<100 × 10^9/L)	2	—	1 (<150 × 10^9/L)
Blood blasts ≥2%	1	1	2 (≥3% blasts)
Fibrosis grade ≥2	1	—	—
Absence of *CALR* type 1 mutation	1	2	2
Presence of HMR mutation	1	1	—
≥2 HMR mutations	2	2	—
Unfavorable karyotype†	—	3	—
Risk group	**Points/5-y OS**	**Points/5-y OS**	**Median survival**
Low	0-1: 95%	0-2: 91%	Low: NR
Intermediate	2-4: 70%	3: 66%	Int-1: 9.3 y
High	≥5: 29%	4-6: 42%	Int-2: 4.4 y
Very high	—	≥7: 7%	High: 2 y

Adapted from Guglielmelli P et al, *J Clin Oncol*. 2018;36(4):310-318; Passamonti F et al, *Leukemia*. 2017;31(12):2726-2731.

†Unfavorable karyotype includes any abnormal karyotype other than normal, sole abnormalities of 20q−, 13q−, +9, chromosome 1 translocation/duplication, −Y, or sex chromosome abnormality other than −Y.

HMR mutations: *IDH1/2, EZH2, ASXL1, SRSF2*.

*Also assigns 0.15 points to any age. Calculators are available in both cases to predict prognosis.

NR, not reached.

in selection of stem cell transplant candidates. Fit patients with higher disease risk may benefit from this intensive and potentially curative approach. Short of transplant, other treatment approaches for MF are geared toward improving symptoms and should be personalized for the individual patient. Symptomatic management may target cytokine-driven constitutional symptoms (fatigue, fever, weight loss, night sweats, pruritus, and bone pain), splenomegaly, and/or cytopenias (Figure 17-6).

Observation

For those with lower-risk MF and a lower symptom burden, an initial period of active observation is often appropriate. Clinicians should monitor for worsening symptom burden (ideally via serial completion of the MPN-10 tool), increasing spleen size, increasing liver size, sequelae (abdominal discomfort, early satiety, weight loss), progressive cytopenias, and increase in peripheral blasts. To date, there is no clear evidence that early initiation of JAK inhibitors or any other therapy for patients with lower-risk, asymptomatic MF improves long-term outcomes. Experimental trials in low-risk PMF and slowly progressive post-ET/PV MF with a goal of delaying disease progression would be reasonable and are being considered with pegylated IFNα or other agents.

Stem cell transplantation

Allogeneic stem cell transplant is the only potentially curative treatment modality for MF. However, this high-risk and high-reward procedure requires careful consideration. Unique transplant challenges in the setting of MF include a generally older patient population at diagnosis, often a decreased performance status or increased comorbidities stemming from MPN sequelae (ie, deconditioning or malnutrition from constitutional symptoms/splenomegaly, cardiovascular disease, pulmonary hypertension, or portal hypertension from splanchnic vessel thrombosis), an abnormal/fibrotic bone marrow microenvironment that may impair engraftment, and splenomegaly that may also delay or impair engraftment. Additional challenges, intrinsic to the transplant procedure, include toxicity from the conditioning regimen, graft failure, graft-versus-host disease, and disease relapse. Transplant outcomes vary widely in MF series, with 5-year overall survival roughly ranging from 30% to 65%.

Selection of the ideal transplant candidate remains challenging, and age/comorbidities, caregiver availability, type of donor, an individual's own risk philosophy, and the prognosis carried by the disease itself factor into decision making. The prognostic scoring systems described previously are integral to weighing the risks of the disease to

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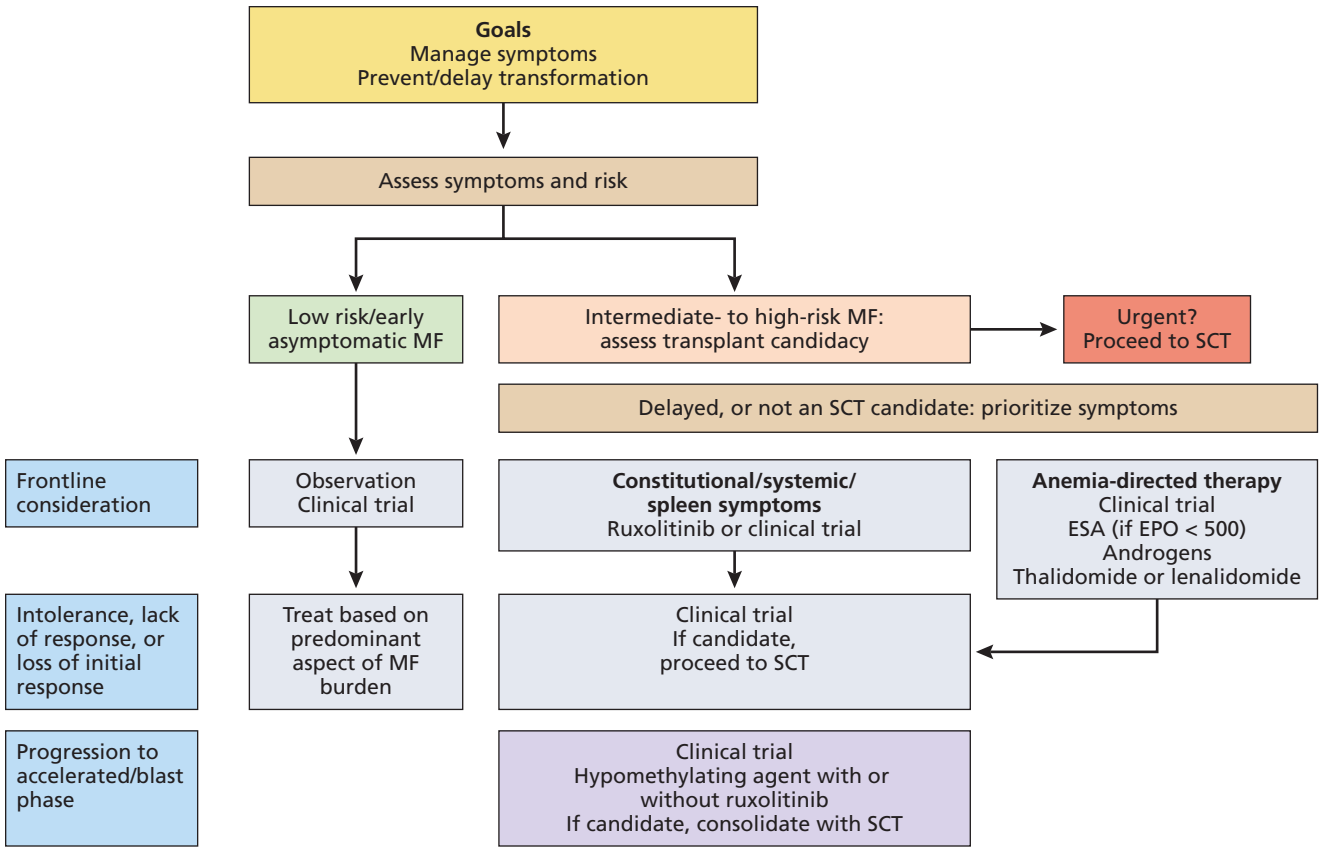

Figure 17-6 MF management algorithm.

compare with the potential risks and benefits of a transplant. Although the expected benefit/risk ratio is more modest among those with more intermediate risk disease, transplant is generally considered in those with higher-risk MF, defined as DIPSS-Plus score >1, MIPSS-70 ≥4, or MIPSS-70+ v2.0 ≥4. In most patients with lower-risk prognostic scores, the risk of transplantation outweighs the benefits.

Novel pretransplant strategies, including the use of JAK inhibition, are under investigation. In the contemporary era, many referred patients have been treated with JAK inhibitors prior to transplant. The rationale includes improving performance status and decreasing splenomegaly; furthermore, there is speculation that modulating the cytokine profile could influence graft-versus-host disease risk. If JAK inhibition is used pretransplant, questions regarding duration and best approach for weaning JAK inhibition prior to transplant or overlapping it with a conditioning regimen remain. Pretransplant treatments may also include iron chelation in those who have required chronic red cell transfusions and cytoreduction in those with an increased blast percentage in the blood or bone marrow.

Symptom-directed management

Predominant cytokine-associated and/or splenomegaly-related symptoms

JAK inhibition. JAK inhibitors are the mainstay of therapy for patients with symptomatic MF. There are currently 2 JAK inhibitors available for use in the United States: ruxolitinib and fedratinib. Both are useful in managing constitutional symptoms and splenomegaly, but their impact on other disease features such as marrow fibrosis, mutant allele burden, and transformation to acute leukemia is minimal at best. Worsening of cytopenias, particularly thrombocytopenia, is an important limitation of JAK inhibitors. It is worth noting that JAK inhibitors can be used regardless of the molecular profile of the disease. JAK-STAT dysregulation is a central pathogenic mechanism in MF regardless of the presence or absence of JAK2 mutations, so the decision to use a JAK inhibitor should be based on the patient's symptoms and clinical presentation and not on mutation status.

Ruxolitinib, a JAK1/JAK2 inhibitor, was the first pharmacologic agent to be FDA-approved in MF. The pivotal phase 3, multicenter, double-blind, placebo-controlled, randomized trial Controlled Myelofibrosis Study with Oral

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JAK-Inhibitor Treatment (COMFORT-I) showed at least a 35% spleen volume reduction. The reduction was assessed by radiologic imaging (magnetic resonance imaging [MRI] or computed tomography [CT] scan) at 24 weeks in 41.9% of patients in the ruxolitinib arm, compared with just 0.7% in the placebo. Furthermore, a decrease in the total symptom score by >50% at 24 weeks was noted in significantly more ruxolitinib-treated patients (45.9%) compared with those receiving the placebo (5.3%). The European counterpart study, COMFORT-II, compared ruxolitinib versus BAT and demonstrated a spleen volume reduction of at least 35% in 28% of patients on ruxolitinib, compared with 0% in patients on BAT at 48 weeks. Similarly, quality-of-life measures and disease-related symptoms were better in the ruxolitinib-treated patients. Five-year follow-up reported a median duration of spleen response of about 3 years. The impact on mutation allele burden has been modest (of unknown significance), as have been histological changes. However, survival benefits have been reported likely owing to changes in performance or functional status rather than through achievement of complete or partial remission.

The main side effects of ruxolitinib include dose-dependent anemia and thrombocytopenia; therefore, these baseline parameters influence dosage. Additional side effects can include headache, bruising, dizziness, diarrhea, weight gain, and increase in cholesterol. Skin cancers and infections (typical and atypical) have also been reported. Additional JAK inhibitors (including pacritinib, momelotinib, and NS-018) are in development in hopes of offering similar or improved clinical efficacy with potentially less myelosuppression. Multiple combination strategies for use with ruxolitinib have also been tested or are ongoing with a hope of demonstrating synergistic effects or offsetting/ameliorating myelosuppression or cytopenias.

Fedratinib, a multikinase inhibitor with selectivity for JAK2 over other JAK family kinases, was approved in 2019 for patients with intermediate-2 or high-risk MF both in the treatment-naïve and previously treated setting. Fedratinib approval was based on the JAKARTA trial, which enrolled patients with higher-risk MF who did not have prior JAK-inhibitor exposure and randomized them to 2 doses of fedratinib (500 mg/d or 400 mg/d) versus placebo. Spleen volume reductions of ≥35% were noted in 36% to 40% of patients treated with fedratinib, compared with only 1% in the placebo group. Symptom reductions of ≥50% were seen in a similar proportion: 34% to 36% on fedratinib compared with 7% on placebo. JAKARTA2 was a single-arm study of fedratinib 400 mg daily in patients with higher-risk MF who had been previously treated with ruxolitinib. Even in this second-line setting, fedratinib was associated with a spleen volume response in 55% of patients and a symptom response in 26% of patients, suggesting a mechanism of action that differs from ruxolitinib.

Like ruxolitinib, one main consideration with fedratinib use and dosage is the potential to worsen anemia and thrombocytopenia. Fedratinib has other unique toxicities as well. Gastrointestinal toxicities, nausea, and diarrhea in particular, can be significant and may occur as early as the first dose. Patients should be counseled in advance about these toxicities, and aggressive supportive care with antiemetics and antidiarrheal agents should be deployed when necessary. An unexpected finding of Wernicke's encephalopathy has been described in a small percentage of patients taking fedratinib perhaps because of thiamine (vitamin B1) malabsorption related to gastrointestinal toxicities. As a result, thiamine levels, overall nutritional status, and close attention to GI toxicities should be observed while patients are on fedratinib.

Splenectomy and splenic radiation. Spleen-directed approaches, like splenectomy and splenic radiation, have limited roles in the era of JAK inhibitors. Splenectomy is associated with a high morbidity and mortality, attributed to abdominal thrombotic events, postoperative hemorrhage, and postsplenectomy leukocytosis and thrombocytosis. However, splenectomy can be considered a salvage option after JAK-inhibitor failure when no other medical or investigational options are present. Low-dose splenic radiation can offer temporary symptomatic relief, but may cause prolonged and serious myelosuppression. This procedure should also be reserved for cases in which no other medical or investigational options are present, and patients and radiation oncologists must be aware of the cytopenia risks.

Rarely, extramedullary hematopoiesis can involve sites other than the spleen or liver, including the vertebral column (paraspinal or intraspinal lesions), which can lead to cord compression; lung, which can associate with pulmonary hypertension; pleura; retroperitoneum; eye; kidney; bladder; mesentery; and skin. Consultation with radiation oncology may be required in some cases.

Cytopenia-directed therapy

MF-associated anemia represents a currently unmet treatment need, even though conventional options have been used. These include erythropoiesis-stimulating agents (ESAs), which can occasionally improve anemia in non-transfusion-dependent patients with EPO levels <500 mIU/mL (especially when <125 mIU/mL). Rarely, splenomegaly may worsen during ESA therapy. Androgens, including danazol, oxymetholone, nandrolone, and testosterone, can lead to anemia or platelet responses in 10% to

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35% of patients. A small subset of patients with evidence of hemolytic anemias can respond to corticosteroids. Immunomodulatory drugs also can have an impact on myelofibrosis-associated anemia perhaps from impact on the intramedullary cytokine milieu, which may inhibit hematopoiesis. Such options include thalidomide/tapering prednisone or lenalidomide/tapering prednisone. Thrombocytopenia responses have also been reported with thalidomide/prednisone. Toxicities can include sedation and neuropathy. Lenalidomide can have activity in MF-associated anemia, particularly in those with a deletion 5q, but can be myelosuppressive. A randomized clinical trial of pomalidomide did not show benefit over the placebo.

A unique feature of momelotinib, a JAK inhibitor currently in clinical trials, is its ability to improve anemia. Elevation of hepcidin, which interferes with iron metabolism and utilization, is thought to play a role in MF-associated anemia. Momelotinib targets ACVR1/ALK2 mediated hepatic production of hepcidin, thus prompting mobilization of storage iron and promoting erythropoiesis.

MPN-accelerated or blast phase

All MPNs carry the risk of transformation to more advanced phase of disease, known as accelerated phase (MPN-AP) or blast phase (MPN-BP). MPN-AP is defined by 10% to 19% blasts in the blood or bone marrow, and MPN-BP is defined by ≥20% blasts in the blood or bone marrow. Transformation generally represents clonal evolution of the underlying disease with acquisition of new cytogenetic or molecular abnormalities. Risk of transformation is highest among those with MF, as compared with those who have ET or PV. Other risk factors for transformation include higher prognostic risk score, leukocytosis, anemia, thrombocytopenia, unfavorable karyotype, and certain additional mutations (ie, *ASXL1, IDH1/2, EZH2, SRSF2).* Prognosis after transformation to MPN-AP or MPN-BP is extremely poor.

MPN-BP is typically refractory to standard induction chemotherapy, as compared with de novo AML. This refractory nature highlights the importance of consideration of stem cell transplant earlier in the course of the disease for individuals with high-risk features. While approximately 40% to 50% of patients with MPN-BP treated with AML-like induction chemotherapy may return to a more chronic phase of an MPN, the duration of disease control is usually short. In this setting, if stem cell transplantation can be performed, it should occur in a rapid fashion. Use of hypomethylating agents, with or without JAK inhibition, is an additional and increasingly used option, whether or not patients will receive stem cell transplant as a means of consolidation. Patients with MPN-AP or MPN-BP should be referred for clinical trial consideration whenever possible.

KEY POINTS

- Myelofibrosis (MF) is a heterogeneous disease spectrum that includes prefibrotic MF, overt primary MF, and post-ET/PV MF.
- Most cases are diagnosed in the seventh decade and beyond, and the prognosis can be quite variable depending on clinical, laboratory, and molecular findings.
- The majority of patients develop anemia, splenomegaly, and significant symptoms during the course of their disease.
- Therapeutic approaches are guided by risk and symptom burden, and stem cell transplantation is an important consideration in selected higher-risk patients.
- JAK inhibitors (ruxolitinib or fedratinib) have been very impactful by decreasing splenomegaly, improving MF-related symptoms, and decreasing disease-associated morbidity and mortality. JAK inhibitors can be used regardless of mutation profile.
- Splenectomy can be considered for palliation in those who are refractory to medical therapies but is employed less frequently in the JAK-inhibitor era.
- Anemia-directed therapies include ESAs, androgens, and immunomodulatory drugs.

Other *BCR-ABL1*–negative MPNs

Chronic neutrophilic leukemia

CLINICAL CASE

A 64-year-old, previously healthy executive noticed a change in her abdominal girth for about 3 months. The symptom was accompanied by bloating, early satiety, occasional nausea, and intermittent episodes of itching. A routine blood test at a local clinic showed the following CBC results: WBCs = 27×10^9/L, Hgb = 12.9 g/dL; hematocrit = 40%; mean corpuscular volume (MCV) = 84 fL, platelet count = 315×10^9/L; and absolute neutrophil count (ANC) = 25×10^9/L. Occasional metamyelocytes and myelocytes were noted accounting for 5% of WBCs, and no myeloblasts were seen. She was referred to a hematologist who noted, by physical examination, hepatosplenomegaly and mild cervical lymphadenopathy. A bone marrow aspiration and biopsy were performed; the results showing increased numbers of neutrophilic granulocytes, a hypercellular marrow (95%), no dysplastic changes, and 3% myeloblasts. Metaphase cytogenetics showed 46, XX [20]. Molecular testing or FISH for *BCR-ABL1*, *PDGFRA*, *PDGRB*, *FGFR1*, *PCM1-JAK2*, and *JAK2* V617F were all unremarkable. Subsequently, her physician sent peripheral blood for *CSF3R* mutation testing, which returned positive findings for a *CSF3R T618I* mutation.

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Introduction

Chronic neutrophilic leukemia is a very rare and chronic MPN, recognized as a distinct entity by the 2016 WHO classification. Historically CNL has been a challenging diagnosis to make, requiring exclusion of reactive neutrophilia and other myeloid malignancies, including typical CML, atypical CML, and chronic myelomonocytic leukemia (CMML). The incidence and prevalence of CNL is difficult to estimate, and males and females appear to be equally affected. Although adolescent patients have been described, CNL occurs more commonly in older patients (often in the seventh decade).

Diagnosis

Although some patients have an incidental discovery of leukocytosis, others present with fatigue and constitutional symptoms, such as weight loss and night sweats. Splenomegaly is the most frequently found clinical feature in patients with CNL. Some patients will present with gastrointestinal tract bleeding, thrombocytopenia, pruritus, and gout. Transformation to acute leukemia has been reported.

CNL is defined by the WHO as having a sustained, nonreactive leukocytosis >25 × 10^9/L, with >80% segmented/band neutrophils, <10% immature granulocytes, <1 × 10^9/L monocytes, and <1% blasts in the peripheral blood. Bone marrow biopsy specimen demonstrates hypercellularity and a striking neutrophil proliferation with a myeloid-to-erythroid ratio reaching up to 20 to 1. Blasts or promyelocytes are not increased in number, and dysplasia and reticulin fibrosis are not evident. Other MPNs should be excluded, and there should be no evidence of *BCR-ABL1*, *PDGFRA/ PDGFRB*, *FGFR1*, or *PCM1-JAK2* mutations. The presence of the *CSF3R* T618I mutation or other *CSF3R* activating mutations has become part of the diagnostic criteria.

Course and prognosis

The clinical course of CNL is heterogeneous. Disease acceleration often manifests with the development of progressive neutrophilia with resistance to previously effective therapy, progressive splenomegaly, worsening thrombocytopenia, or with cytogenetic-clonal evolution. Transformation to blast phase (AML) was reported to occur in a significant proportion of patients at a median of 21 months from diagnosis. Progressive neutrophilia associated with anemia and thrombocytopenia has been reported as transformation to myelodysplasia. Although CNL is regarded as a relatively slowly progressive disease with survival ranging from 6 months to >20 years, one retrospective analysis of 40 patients with CNL reported a median survival time of 23.5 months. Most common causes of death included intracranial hemorrhage (N = 9), progressive disease (N = 5), blastic transformation (N = 4), infection (N = 1), and treatment-related complications (N = 1).

Management

Optimal treatment of patients with CNL remains to be defined. Splenectomy has resulted in worsening of neutrophilic leukocytosis and is not routinely recommended. To date, treatment of CNL has consisted largely of cytoreductive agents like HU, which can improve neutrophilia, symptoms, and splenomegaly; however, these responses often lack durability. Similar to other chronic MPNs, interferons (ie, IFNα) have been used. Allogeneic hematopoietic cell transplantation (HCT) can be curative but is usually reserved for patients with accelerated or blastic transformation. Given the potential for blastic transformation and progressive refractory neutrophilia, however, allogeneic hematopoietic cell transplantation may be appropriate earlier in the disease course for younger patients. In the first report of *CSF3R* mutations in CNL, Maxson et al described a single patient with a membrane proximal mutation (*CSF3R* T618I), and improvement in neutrophilic leukocytosis and thrombocytopenia when treated with ruxolitinib. In another report, a patient with a membrane proximal mutation (also *CSF3R* T618I) and a *SETBP1* mutation was refractory to ruxolitinib and HU. The safety and efficacy of ruxolitinib in CNL (and atypical CML) have been investigated in a multicenter study (clinical trials identifier: NCT02092324), demonstrating a response rate of 32%. Ruxolitinib has also been found to be active in a mouse model of CNL. No reports have been published detailing the clinical utility of dasatinib in CNL or atypical CML harboring truncation mutations in *CSF3R*.

Chronic eosinophilic leukemia, not otherwise specified

CLINICAL CASE

A 35-year-old male graduate student came to the university health clinic because of nonproductive cough, diarrhea, fatigue, intermittent fevers (102 °F [38.9 °C]), and muscle aches. He initially attributed these symptoms to stress, but sought medical attention because of persistence over a 2-month period. A CBC showed WBCs = 19 × 10^9/L,

Clinical Case continues

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CLINICAL CASE *(continued)*

Hgb = 11.5 g/dL, MCV = 83 fL, platelets = 188×10^9/L, ANC = 12×10^9/L, and absolute eosinophil count (AEC) = 3.4×10^9/L. There were 3% circulating blasts in the peripheral blood. Workup for connective tissue diseases, parasitic infections, and allergies was unremarkable. His subsequent examination by a hematologist confirmed an eosinophilic leukocytosis and a bone marrow aspiration, and biopsy results showed 6% bone marrow blasts with no dysplastic changes. Metaphase cytogenetics were normal (46,XY [20]). The evaluation had no abnormal findings in *PDGFRA*, *PDGFRB*, *FGFR1*, *PCM1-JAK2*, or *BCR-ABL1*.

Chronic eosinophilic leukemia is characterized by an autonomous, clonal proliferation of eosinophil precursors resulting in persistent elevation of eosinophils in the peripheral blood, bone marrow, and peripheral tissues. Although CEL, not otherwise specified (CEL-NOS), is a rare MPN, the true incidence of these neoplasms is unknown. Nonetheless, myeloproliferative eosinophilic syndromes seem to occur much more often in men than in women. The peak incidence is in the fourth decade, but CEL-NOS can occur at any age, including childhood.

Clinical features and diagnostic criteria

A minority of patients with CEL-NOS are singled-out incidentally. More commonly, patients present with fever, fatigue, cough, pruritus, diarrhea, angioedema, and muscle pain. End-organ damage can be a manifestation of a direct eosinophilic infiltrate or secondary to the release of cytokines and the contents of toxic granules. The most serious clinical findings relate to endomyocardial fibrosis resulting from eosinophilic infiltration of the heart, leading to constrictive pericarditis, fibroblastic endocarditis, myocarditis, or intramural thrombus formation (owing to scarring of the mitral or tricuspid valves). Peripheral and central nervous system findings can include mononeuritis multiplex, peripheral neuropathy, paraparesis, cerebellar involvement, epilepsy, dementia, cerebral infarction, and eosinophilic meningitis. Pulmonary involvement includes idiopathic infiltrates, fibrosis, pulmonary effusions, and pulmonary emboli. Skin manifestations are common and can take many forms, including angioedema, urticaria, papulonodular lesions, and erythematous plaques. Gastrointestinal involvement by eosinophilia can result in ascites, diarrhea, gastritis, colitis, pancreatitis, cholangitis, or hepatitis.

The WHO criteria for diagnosis of CEL-NOS require the presence of eosinophilia (1.5×10^9/L); a clonal cytogenetic or molecular abnormality or blasts cells >2% in the peripheral blood or >5% in the bone marrow; lack of *BCR-ABL1*, *PDGFRA*/*PDGFRB*, *FGFR1*, or *PCM1-JAK2* rearrangements; bone marrow blasts <20%; and the absence of inv(16)(p13.1q22). Consideration for idiopathic hypereosinophilic syndrome (HES) requires exclusion of patients with infectious, allergic, autoimmune, collagen vascular disorders, pulmonary conditions, or neoplastic conditions (including clonal-lymphoid disorders), which are known to be associated with secondary eosinophilia. Therefore, Idiopathic HES is classified in patients who have the following characteristics: (1) persistent eosinophilia (>1.5×10^9/L) lasting for at least 6 months (although this is in evolution because treatment needs can be urgent, and waiting 6 months is inappropriate); (2) no reactive causes of eosinophilia; (3) no associated clonal myeloid neoplasm like AML, MDS, MDS/MPN overlap, MPN, and systemic mastocytosis; (4) no cytokine-producing immunophenotypically aberrant T-cell population; (5) no increased myeloblasts in the peripheral blood or bone marrow; and (6) no evidence of eosinophil clonality and with end-organ damage. If the previous 6 criteria were fulfilled, except that there is no end-organ damage, then it's best classified as idiopathic hypereosinophilia. Panels using next-generation sequencing targeting genes commonly mutated in myeloid malignancies can be helpful because once clonality is establish, cases of HES can be redefined as CEL-NOS.

Course and prognosis

CEL-NOS typically carries a poor prognosis. Blast transformation can occur, and poor prognostic features include marked splenomegaly, cytogenetic abnormalities, and dysplastic myeloid features in the bone marrow. In a report on 10 patients with CEL-NOS, the median overall survival was 22 months, and one-half transformed to acute leukemia at a median of 20 months from the time of diagnosis. Idiopathic HES can have a variable course and tends to be a chronic disorder. In one series, including patients with idiopathic HES and eosinophilic leukemia, 80% of patients were alive at 5 years after diagnosis and 42% were alive at 15 years.

Management

Treatment is indicated for patients with evidence of end-organ damage. Therapy for CEL-NOS and idiopathic HES is aimed primarily at decreasing the eosinophil count, improving symptoms, and preventing end-organ damage or thromboembolic complications. Inadequate data exist to support initiation of therapy based on a specific eosinophil count in the absence of organ disease. Corticosteroids (eg, prednisone 1 mg/kg/d) have typically been the

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treatment of choice in HES to reduce eosinophil numbers and minimize the cytotoxic effects of the eosinophilic granules. Steroid-resistant patients traditionally have been treated with HU. IFNα can elicit sustained hematologic and cytogenetic remissions in idiopathic HES and CEL-NOS that has been refractory to other therapies, including prednisone and HU. In one retrospective study where 46 patients were treated with IFNα, the response rates were 50% and 75% for monotherapy or in combination with steroids, respectively. Lack of steroid responsiveness, or failure of HU or IFNα, may warrant consideration of cytotoxic chemotherapeutic agents such as vincristine, cyclophosphamide, or etoposide. Imatinib is also a consideration, but expectations regarding response rates and duration are much lower compared with those patients who possess *PDGFRA* or *PDGFRB* rearrangements.

Anti–IL-5 antibody approaches, such as mepolizumab, have been undertaken in HES based on the cytokine's role as a differentiation, activation, and survival factor for eosinophils. Long-term results have been presented in 78 patients who had a median exposure of 251 weeks. Ninety-seven percent of patients experienced adverse effects, but approximately one-third were considered drug-related. Cough, fatigue, headache, upper respiratory tract infections, and sinusitis were the most commonly observed side effects. Suppression of eosinophilia was noted, and in the first 4 months, the median prednisone dose decreased from 20 to 0 mg (1.8 mg was the median dose over the course of the study). Although it has regulatory approval for the treatment of certain subsets of asthma and eosinophilic granulomatosis with polyangiitis, mepolizumab is not approved for CEL-NOS at the time of this writing, but it is available in a clinical trial (ClinicalTrials.gov identifier: NCT02836496).

Use of the anti-CD52 monoclonal antibody alemtuzumab in refractory HES, based on the expression of the CD52 antigen on eosinophils, has also been reported. A study that included 11 patients with HES and CEL used alemtuzumab in escalating doses of 5, 10, and 30 mg intravenously from days 1 to 3, then maintained at the tolerated dose 3 times per week for a total of 12 doses. The regimen resulted in a 91% complete hematologic response after a median of 2 weeks. The median duration of response was 3 months. A second retrospective study of 12 patients with HES or CEL treated with alemtuzumab reported a complete hematological response in 10 (83%) for a median of 66 weeks. Eleven relapses were reported and 5 achieved a second complete hematological response with retreatment. Infusion reactions and viral infections reported include cytomegalovirus, zoster, and Epstein-Barr virus. Despite these results, the data on alemtuzumab remain limited, and the drug is best considered an investigational therapy for this condition at this time.

Myeloproliferative neoplasm, unclassifiable

The term *MPN, unclassifiable* (MPN-U) should be used to describe only those patients who meet clinical, laboratory, and morphologic criteria of MPNs but who fail to present features of any single MPN entity or patients who present with overlapping features of 2 or more MPN entities. The demonstration of pathognomonic molecular abnormalities, like *BCR-ABL1* fusion or the *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2* rearrangements, excludes the diagnosis of MPN-U. In the era of molecular diagnostics, it is expected that the number of MPN-U will likely decrease. The exact incidence, median age at onset, and sex distribution of MPN-U are not truly known.

Clinical features

The clinical features of patients with MPN-U are variable because this is a heterogeneous group of disorders. Patients can present with minimal to no organomegaly and well-preserved peripheral blood counts in the very early stages of the disease or massive organomegaly, extensive myelofibrosis, and severe cytopenias in advanced cases. Unexplained portal or splanchnic vein thrombosis may be the initial presenting feature in these patients.

Course and prognosis

The clinical course and prognosis for patients with MPN-U can be extremely heterogeneous. Patients with early-stage disease can safely be actively observed, and often develop features of a unique MPN entity over time. Patients in whom unique MPN entities are no longer recognizable tend to have aggressive clinical courses and very poor prognosis.

Systemic mastocytosis

CLINICAL CASE

A 67-year-old retired woman has been experiencing fever, chills, diarrhea, a persistent urticaria-like rash, flushing, and palpitations for the past 5 months. She decided to see a primary care physician, who noticed palpable lymph nodes in the neck and axillary regions and a palpable spleen tip by physical examination. Routine blood work showed normocytic anemia (Hgb = 10.1 g/dL, MCV = 92 fL); leukocytosis (WBCs = 25×10^9/L) with increased lymphocytes (40%), monocytes (28%), and eosinophils (12%); and mild thrombocytopenia (platelets = 97×10^9/L). Review of blood work 6

Clinical Case continues

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CLINICAL CASE *(continued)*

months prior showed similar CBC findings. The patient saw a hematologist and underwent a bone marrow aspiration and biopsy, the results of which showed dysplastic changes in the erythroid and megakaryocytic lineages with 5% blasts in the bone marrow. The biopsy specimen showed a hypercellular marrow with spindle-shaped mast cell infiltration grade of 50%. Flow cytometry of the bone marrow aspirate showed increased CD25 expression on mast cells. A *KIT*D816V mutation also was identified. Metaphase cytogenetics showed 46, XX [20]. Total tryptase level was 450 ng/mL. The patient was diagnosed with systemic mastocytosis with an associated hematological neoplasm (SM-AHN), specifically chronic-myelomonocytic leukemia (CMML-1).

Mastocytosis encompasses a heterogeneous spectrum of disorders characterized by mast cell proliferation and accumulation (Figure 17-7). Clinical manifestations of mast cell disorders are caused by uncontrolled proliferation of tissue mast cells and the release of mast cell-derived mediators. While cutaneous mastocytosis (CM) is usually a chronic, indolent disease, SM can be either indolent or more aggressive and even life threatening. Given that SM has a spectrum of clinicopathologic features in common with MPNs, the 2008 WHO classification included SM under the broader umbrella of MPNs. However, in 2016, it was moved to its own category. Mastocytosis can be classified according to clinicopathologic and laboratory findings (Table 17-16). Indolent SM usually has a low burden of disease, and smoldering SM is characterized

Figure 17-7 Bone marrow involvement with systemic mastocytosis. (A) Marrow biopsy results show areas of scattered infiltration or complete replacement by elongated, spindle-shaped cells (hematoxylin-and-eosin stain; original magnification, 85×). Photo courtesy of Steven J. Kussick (University of Washington, Seattle, WA). (B) Mast cells stain test positive (brown) for tryptase. Serum tryptase level was elevated at 45.9 ng/mL (200×). Source: ASH Image Bank/Ganesh Chandrasekhar Kudva and Leonard E. Grosso. (C) Spindle-shaped mast cells on a bone marrow aspirate. Source: ASH Image Bank/Sylvie Bouvier and Anne Arnaud.

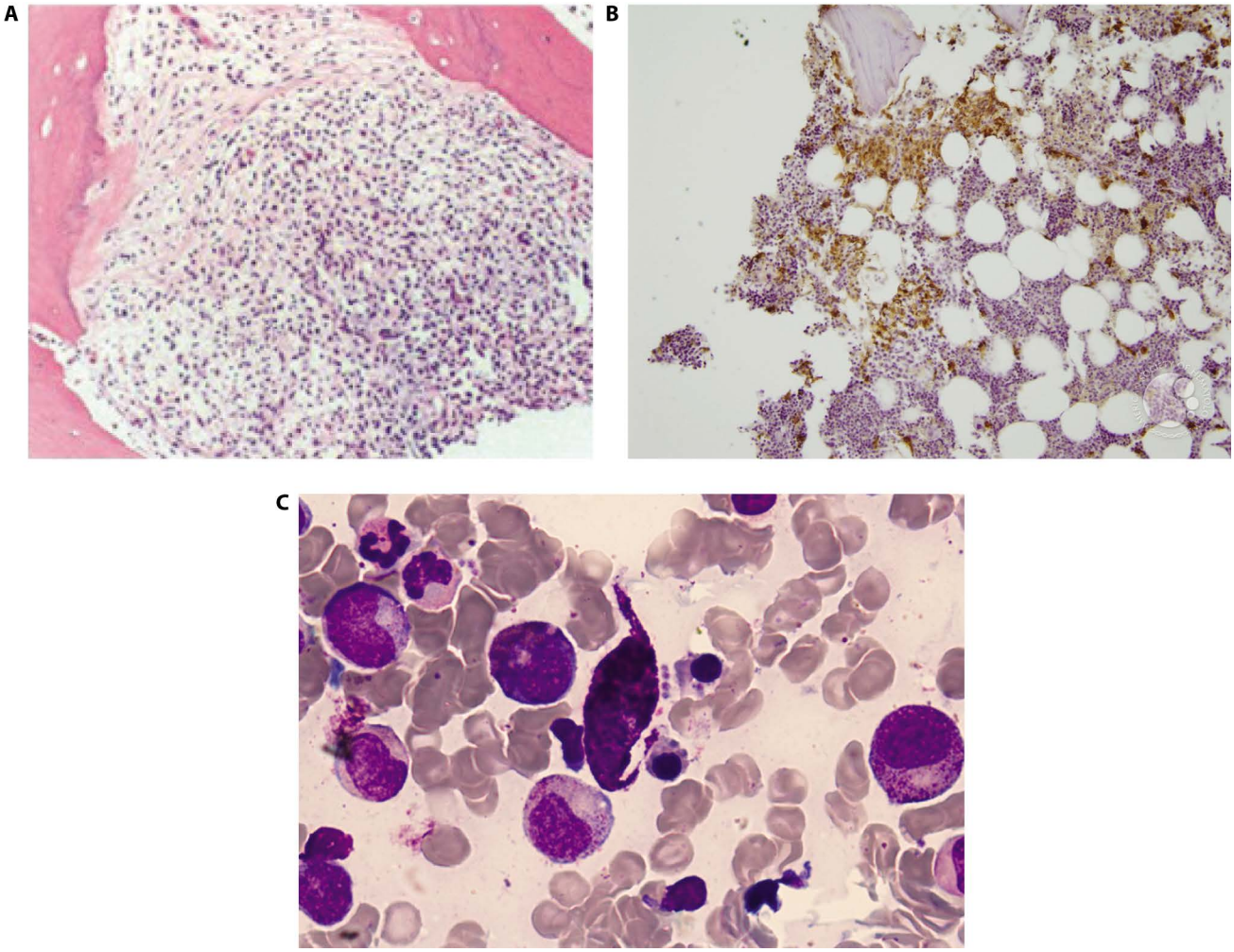

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Table 17-16 The 2016 WHO classification of mastocytosis

1. CM
2. Systemic mastocytosis
   a. Indolent systemic mastocytosis*
   b. Smoldering systemic mastocytosis*
   c. SM-AHN
   d. ASM*
   e. MCL
3. Mast cell sarcoma

Adapted from Arber DA et al, *Blood*. 2016;127(20):2391-2405.

*These subtypes require information regarding B and C findings for complete diagnosis, all of which may not be available at the time of initial tissue diagnosis.

by 2 or more B findings (Table 17-17). Advanced SM is an umbrella term encompassing aggressive SM (ASM), SM-AHN, and mast cell leukemia (MCL). ASM is defined by one or more C findings (indicating organ damage), and SM-AHN and MCL also usually exhibit C findings (Table 17-17). MCL is histopathologically defined as 20% or more neoplastic mast cells on a bone marrow aspirate. In contrast to more indolent SM, advanced SM typically exhibits shortened survival and usually requires cytoreduction. The incidence of mastocytic disorders is poorly defined, and SM is felt to be a very rare disease. Although mastocytosis can be diagnosed at any age, CM is more common in children; whereas, SM occurs predominantly in adults. These disorders appear to have a slight male predominance.

Pathobiology

Mast cells are long-lived hematopoietic cells with unique biologic properties and a unique spectrum of mediators and cell surface antigens. Mature mast cells are best known for their involvement in allergic inflammation mediated by allergen-specific immunoglobulin E (IgE) and tend to reside in diverse organs, often in close vicinity to smaller or larger blood vessels. Mast cell survival depends largely on stem cell factor. KIT is the protein tyrosine-kinase receptor for SCF.

Other somatic mutations, including *TET2*, *DNMT3A*, *ASXL1*, *SF3B1*, and *CBL* mutations, also have been identified in a subset of patients with mastocytosis, particularly in those with an associated hematological nonmast cell disease (SM-AHN). In a study of 39 *KIT* D816V-mutated SM patients, Schwaab et al reported that the presence of additional somatic mutations (most frequently *TET2*, *SRSF2*, *ASXL1*, *CBL*, and *RUNX1*) were more common in those with advanced SM and contributed to inferior survival (the S/A/R profile in particular, referring to mutations in *SRSF2*, *ASXL1*, or *RUNX1*). When SM is diagnosed in conjunction with another hematologic neoplasm (~30%-40% of cases), the underlying neoplasm is typically of myeloid rather than lymphoid origin. Mutations in *KIT* D816V have been identified in both the mast cell and associated hematological non–mast cell lineage disease (AHNMD) compartment, which potentially may indicate a shared pathogenetic origin in a hematopoietic progenitor. Patients with indolent systemic mastocytosis appear to have more of a pure *KIT* D816V-driven disease. Apart from organ infiltration, the consequences of mastocytosis stem from mediator release because mast cells are activated and degranulate. Mast cells contain a variety of mediators, including histamine, inflammatory cytokines such as IL-3 and IL-16, and tumor necrosis factor. In addition, mast cells contain secretory granule proteases, most commonly tryptase, which is increased in mast cell diseases. An increase in tryptase levels serves as a minor criterion for diagnosis (unless AHNMD is present). Although the level itself cannot distinguish SM subgroups, marked increases are seen in more advanced/aggressive subtypes. Additionally, measurement serves as a practical means of assessing mast cell burden and monitoring response to therapy.

Clinical features and diagnosis

Clinical features at the time of presentation for patients with mastocytosis depend on the extent of organ infiltration, consequences of mediator release, and whether a nonmast cell disorder is also present. Cutaneous manifestations of mastocytosis typically include a reddish-brown maculopapular eruption (urticaria pigmentosa) or, less often, a diffuse erythema, plaques, or nodules. The classic description of urticaria, following stroking of the skin, is coined the "Darier sign." Telangiectasia macularis eruptiva perstans, characterized by red-brown macules with irregular borders and a telangiectasia-like appearance, is a less common cutaneous manifestation. Cutaneous manifestations may be the only consequence of mast cell disease in children. Blistering can occur in pediatric patients and represents an aggressive form of urticaria pigmentosa.

Mastocytosis is typically systemic in adults and often includes bone marrow infiltration. Other organs commonly involved include the liver, spleen, lymph nodes, and gastrointestinal mucosa. Clinical features of SM are categorized in 4 distinct groups: (1) constitutional symptoms (eg, fatigue, fever, weight loss); (2) cutaneous manifestations, as described previously; (3) systemic mediator-related symptoms (eg, abdominal pain or bloating, dyspepsia, diarrhea, flushing, headache, hypotension, anaphylaxis); and (4) musculoskeletal complaints (eg, bone pain and myalgias, osteopenia, fractures). Anaphylaxis after a Hymenoptera (ie, bee or wasp) sting can also indicate underlying mastocytosis, and a workup for mast cell disease is warranted.

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Table 17-17 WHO criteria for diagnosis of cutaneous and systemic mastocytosis

Cutaneous mastocytosis
Skin lesions demonstrating the typical clinical findings and typical infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy. Absence of features/criteria for the diagnosis of SM
Systemic mastocytosis
The diagnosis of SM may be made if 1 major criterion and 1 minor criterion are present or if 3 minor criteria are fulfilled
Major criterion
Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)
Minor criteria
a. In biopsy specimen sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical mast cells
b. Detection of *KIT* point mutation at codon 816 in bone marrow, blood, or other extracutaneous organ(s)
c. Mast cells in bone marrow, blood, or other extracutaneous organs that coexpress CD117 with CD2 and/or CD25
d. Serum total tryptase persistently >20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)
Indolent systemic mastocytosis
Meets criteria for SM
No evidence of an associated clonal hematologic non–mast cell lineage disease
No "C" findings
Mast cell burden is low, and skin lesions are almost invariably present
• Bone marrow mastocytosis: bone marrow involvement, but no skin lesions
• Smoldering systemic mastocytosis: with 2 or more "B" findings but no "C" findings
Aggressive systemic mastocytosis
Meets criteria for SM
One or more "C" findings
No evidence of mast cell leukemia
• Lymphadenopathic mastocytosis with eosinophilia (provisional subvariant): progressive lymphadenopathy with peripheral blood eosinophilia, often with extensive bony involvement and hepatosplenomegaly, but usually without skin lesions. Exclude cases with rearranged *PDGFRA*.
Systemic mastocytosis with associated clonal hematologic non–mast cell lineage disease
Meets criteria for SM
Associated clonal hematologic nonmast cell lineage disorder (MDS, MPN, AML, lymphoma, or other hematologic neoplasm that meets the criteria for a distinct entity in the WHO classification)
Mast cell leukemia
Meets criteria for SM
Diffuse bone marrow infiltration by atypical immature mast cells. Bone marrow aspirate contains >20% mast cells. Usually >10% circulating mast cells on peripheral blood.
"B" findings
1. Bone marrow biopsy results showing >30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level >20 ng/mL
2. Signs of dysplasia or myeloproliferation in nonmast cell lineage, but insufficient criteria for definitive diagnosis of hematopoietic neoplasm by WHO, with normal or only slightly abnormal blood counts
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or palpable or visceral lymphadenopathy

Table continues on next page

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Table 17-17 WHO criteria for diagnosis of cutaneous and systemic mastocytosis *(continued)*

"C" findings
1. Bone marrow dysfunction manifested by one or more cytopenia (ANC $<1 \times 10^9$/L, Hgb <10 g/dL, or platelets $<100 \times 10^9$/L), but no frank nonmast cell hematopoietic malignancy
2. Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
3. Skeletal involvement with large-sized osteolysis and/or pathologic fractures
4. Palpable splenomegaly with hypersplenism
5. Malabsorption with weight loss because of gastrointestinal mast cell infiltrates

Adapted from Horny HP et al. In: Swerdlow SH et al, eds, World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. (IARC Press; 2008).

The diagnosis of CM is confirmed by the demonstration of pathologic mast cell infiltration of the skin. SM requires involvement of at least one extracutaneous tissue by clonal mast cells (bone marrow is the most commonly involved organ). Diagnostic criteria for CM, SM, and variant presentations of SM are summarized in Table 17-17.

Course and prognosis

Life expectancy can be quite variable, ranging from only a few months in aggressive SM variants to nearly normal life spans in more indolent disease. CM in children tends to have an indolent course and often is associated with spontaneous regression. Adults with CM rarely may evolve to SM. The presence of cutaneous involvement in SM appears to confer an indolent behavior; whereas, lack of skin involvement is associated with aggressive behavior. Predictive factors of poor prognosis in SM include older age at onset of symptoms, absence of CM, low platelets, hypoalbuminemia, hepatosplenomegaly, anemia, and elevated LDH.

Management

Treatment of CM includes H_1 and H_2 antihistamines, cromolyn, other mast cell stabilizers, topical or intralesional glucocorticoids, psoralen, and UV-A phototherapy. Adults with chronic CM may require long-term continuous or intermittent symptomatic treatment.

For adult patients with indolent variants of SM, treatment of mediator-related symptoms with combinations of H_1 and H_2 antihistamines, leukotriene antagonists, proton pump inhibitors, cromolyn, and other mast cell stabilizers may be sufficient to alleviate symptoms. Patients with SM should carry epinephrine in an injectable form available at all times for treating anaphylaxis. Aspirin and nonsteroidal anti-inflammatory drugs have been helpful for some patients with flushing and syncope, but hypersensitivity to these drugs is relatively common and must be excluded. Accordingly, a major goal in the management of mastocytosis is the avoidance of known triggers. Triggers can include opioid analgesics, like morphine and codeine, which are known mast cell degranulators, as well as anesthesia, stress, and infection. Off-label use of IFNα can be helpful for patients with painful skeletal lesions or mast cell tumors that threaten bony integrity. Those with osteoporosis can be treated with calcium and/or bisphosphonate therapy when indicated. Patients with severe or refractory mediator-related symptoms can be considered for cytoreductive therapy.

The aggressive variants of SM may progress to end-stage organ fibrosis or failure and may be complicated by pathologic fractures, severe cytopenias, or a combination of both. Patients with evidence of end-organ damage without major bony complications may benefit from off-label use of IFNα with or without corticosteroids (in cases with incipient end-organ damage); although, most responses are only partial. More rapid cytoreduction is seen with single-agent cladribine, given at 5 mg/m^2/d or 0.13 to 0.17 mg/kg/d as a 5-day treatment cycle every 4 to 6 weeks, which has induced clinical and laboratory responses (ie, decreased serum tryptase and urinary histamine metabolites) in patients with symptomatic SM. Patients receiving cladribine require close follow-up for supportive care because of the myelosuppressive effects of the treatment.

The crucial role of KIT in normal mast cell development and the evidence that *KIT* mutations may be important in SM pathogenesis prompted treatment of mastocytosis patients with tyrosine-kinase inhibitors (TKIs). Because of its inhibitory properties against KIT, imatinib was the first to enter the clinical arena and has regulatory approval in patients who lack the *KIT* D816V mutation. The presence of *KIT* D816V mutation confers resistance to imatinib by affecting the catalytic pocket of the *KIT* protein, preventing imatinib from binding and exerting its inhibitory activity. Therefore, *KIT* mutation analysis is important in therapeutic decision making with SM. A trial of imatinib should be considered for those with aggressive SM who lack the D816V mutation or whose *KIT* mutation status is unknown.

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Midostaurin is a multikinase inhibitor that has displayed potent activity against both wild-type and mutant *KIT*. On this basis, an open-label study of midostaurin 100 mg twice a day in continuous 28-day cycles until progression or intolerable toxicity for patients with aggressive SM was conducted. The overall response rate was 60%, including a major response rate of 45% and partial response rate of 15%. Major response was defined as normalization of ≥1 SM-related organ damage findings (C findings) such as albumin levels, resolution of liver transaminitis, other liver function tests, relief of ascites and pleural effusion, improvement of hemoglobin and platelet levels, and reversal of weight loss. The median duration of response was not reached in patients with ASM or MCL, and it was 12.7 months for patients with SM-AHN. The median overall survival was 44.4 months in responders and 15.4 months for nonresponders (28.7 months for all patients). The median change in mast cell burden, measured by reduction in tryptase, was 57%. The most clinically relevant treatment-emergent toxicities were nausea, vomiting, diarrhea, and myelosuppression, especially in patients with preexisting cytopenias. Based on the results of this study, midostaurin was granted regulatory approval for the treatment of advanced SM. Avapritinib is a potent and selective KIT inhibitor that was FDA-approved for advanced SM in June of 2021. Across all advanced SM subtypes in the phase 1 and phase 2 single-arm studies of avapritinib, the overall response rate was 57%. Approximately half of patients had received prior midostaurin. Responses occurred relatively quickly (median time to response 2 months) and were quite durable (median duration of response 38 months, range 19 months to not reached).

In the setting of relapsed or refractory disease, despite cladrabine and/or KIT inhibitors and those who progress to mast cell leukemia, consideration of clinical trial participation or multiagent antileukemic chemotherapy is appropriate. Allogeneic HCT should be considered for younger patients with aggressive SM who achieve a remission with chemotherapy. In a retrospective analysis of 57 patients, 28% achieved complete remission after transplant. For all subtypes the overall survival was 57% at 3 years, including 74% for SM-AHN, 43% for ASM, and 17% for mast cell leukemia. The diagnoses of MCL (versus others) and reduced-intensity conditioning regimens (versus myeloablative) were associated with an inferior OS.

Symptomatic SM in the presence of a nonmast cell hematologic neoplasm should be treated as indicated both for the hematologic malignancy and for the SM complications. Generally, the underlying non-SM malignancy determines the overall clinical course; however, in cases in which aggressive forms of SM coexist with low-grade myeloid neoplasms, the aggressive SM may take precedence.

Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, *FGFR1*, or *PCM1-JAK2*

The WHO recognizes 3 rare conditions classified as myeloid/lymphoid neoplasms associated with marked and persistent eosinophilia and chromosomal rearrangements, leading to constitutive activation of the *PDGFRA/PDGFRB*, *FGFR1*, or *PCM1-JAK2* genes (Table 17-18).

These are separate entities from CEL and from HES, which are subcategories of MPNs. Although the partner gene involved heavily influences the clinical features, separate consideration needs to be given to *PDGFRA*- and *PDGFRB*-rearranged eosinophilic disorders because they carry major therapeutic relevance owing to the exquisite sensitivity to imatinib therapy.

Table 17-18 Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia

Disease	Presentation	Genetics	Treatment
PDGFRA	Eosinophilia ↑ Serum tryptase ↑ Marrow mast cells	Cryptic deletion at 4q12 *FIP1L1-PDGFRA*, at least 7 other partners	Respond to TKI
PDGFRB	Eosinophilia Monocytosis mimicking CMML	t(5;12)(q32;p13.2) *ETV6-PDGFRB*, at least 30 other partners	Respond to TKI
FGFR1	Eosinophilia Often presents with T-ALL or AML	Translocations of 8p11.2 *FGFR1*-various partners	Poor prognosis; do not respond to TKI
PCM1-JAK2	Eosinophilia Rarely presents with T-ALL or B-ALL Bone marrow shows left-shifted erythroid predominance and lymphoid aggregates	t(8;9)(p22;p24.1) *PCM1-JAK2*	May respond to JAK2 inhibitors

Adapted from Arber DA et al, *Blood*. 2016;127(20):2391-2405.

B-ALL, B cell acute lymphocytic leukemia; T-ALL, T cell acute lymphocyctic leukemia.

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Myeloid/lymphoid neoplasms with *PDGFRA* or *PDGFRB* rearrangements

CLINICAL CASE

A 52-year-old mechanic experienced a stroke of unclear etiology, followed by recurrent headache, rhinorrhea, wheezing, weight loss of 15 lb (~7 kg), diarrhea, night sweats, pruritus, and lower-extremity edema. He underwent a routine blood test, including a CBC, which showed WBCs = 15×10^9/L, Hgb = 10.3 g/dL, MCV = 89 fL, and platelets = 224×10^9/L. The most notable feature on the white blood cell differential was an eosinophilia with an AEC of 2.7×10^9/L. There were no circulating blasts in the peripheral blood. Workup for an underlying connective tissue disease, other neoplastic process, and parasitic infection was negative. A CT scan of the sinus revealed thickening of the right sphenoid sinus. Total IgE was elevated (IgE = 283 kU/L). A CT of the chest showed patchy opacities consistent with bronchiolitis or vasculitis. A CT scan of the abdomen and pelvis confirmed splenomegaly. Transthoracic echocardiography showed a diminished ejection fraction of 30% and the presence of restrictive cardiomyopathy. FISH for the *CHIC2* deletion, a surrogate for the *FIP1L1-PDGFRA* fusion, tested positive in 56% of cells.

Although the true incidence of *PDGFRA*-related neoplasms is not known, it is clear these are rare hematologic disorders. These neoplasms are considerably more common in men than in women (male-to-female ratio, 9:1 to 17:1) and usually are diagnosed between the ages of 25 and 55 years (median age of onset is late 40s). Approximately 5% to 10% of patients in industrial countries who present with idiopathic hypereosinophilia can be found to have the *FIP1L1PDGFRA* fusion. Similarly, *PDGFRB*-related neoplasms are extremely uncommon disorders, and the true incidence of it is not completely known. In fact, among >56,000 cytogenetically defined cases from the Mayo Clinic, only 0.04% exhibited the t(5;12) translocation. In another prospective study, of 556 cases with MPN, only 10 with *PDGFRB* rearrangements were noted. *PDGFRB*-related neoplasms are more common in men than in women (male-to-female ratio, 2:1) with a median age of onset in late 40s.

Pathobiology

PDGFRA and PDGFRB are members of the class III receptor tyrosine-kinase family, which also includes KIT and FLT3. The pathobiology of these molecular lesions is described in the "Driver mutations" section of this chapter.

Clinical features and diagnosis

PDGFRA- and *PDGFRB*-related neoplasms are multisystem disorders associated with bone marrow and peripheral blood eosinophilia. The most common presenting signs and symptoms are weakness, fatigue, cardiopulmonary symptoms, myalgias, rash, and fever. Splenomegaly is a common finding, with a minority of patients also presenting with hepatomegaly. Organ damage occurs because of release of cytokines or direct organ infiltration by eosinophils and possibly mast cells. The most serious complication of *PDGFRA*- and *PDGFRB*-related neoplasms is cardiac in nature, including endomyocardial fibrosis with ensuing restrictive cardiomyopathy.

The most prominent diagnostic feature of cases of *PDGFRA*-related neoplasms is the presence of peripheral blood mature eosinophilia. An elevated serum tryptase is usually also present. Bone marrow biopsy results demonstrate marked hypercellularity with increased mature and precursor eosinophils. It is important to note that *FIPL1-PDGRFA* rearrangements are not exclusively associated with an MPN phenotype because these rearrangements are also associated with presentations of acute leukemia. Fibrosis can be present. Immunophenotyping is typical for activated eosinophils with expression of CD23, CD25, and CD69. The gold standard for the diagnosis of these neoplasms is demonstration of the fusion gene. As mentioned, most cases of CEL-NOS present with normal karyotype; thus, FISH and reverse transcription-polymerase chain reaction (RT-PCR) are preferred methods of testing. FISH testing relies on the probe for the *CHIC2* gene, which is deleted uniformly in patients with the *FIP1L1-PDGFRA* fusion gene. RT-PCR can be used in cases with a high clinical suspicion and negative FISH testing results. RT-PCR is also used for monitoring of disease response and for minimal residual disease testing.

Patients with *PDGFRB*-related neoplasms tend to present with anemia and thrombocytopenia, along with leukocytosis neutrophilia or monocytosis. Features characteristic of CMML, including a monocytic leukocytosis with associated eosinophilia, are often seen. Confirmation of diagnosis for *PDGFRB*-related neoplasms requires demonstration of MPN with prominent eosinophilia and occasional neutrophilia, monocytosis and the presence of the *ETV6- PDGFRB* fusion gene, or an alternative *PDGFRB* gene rearrangement. The classic t(5;12) (q31-q33;p13) can be detected easily by conventional metaphase analysis, so FISH or RT-PCR usually is used for the confirmation of diagnosis and determination of the fusion gene. The bone marrow is hypercellular with increased fibrosis, and mast cells can be increased in number.

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Course and prognosis

In the preimatinib era, the prognosis of patients with *PDGFRA*- or *PDGFRB*-related neoplasia was poor. The median survival did not exceed 1 to 2 years. Patients generally had advanced disease, with congestive heart failure accounting for 65% of the identified causes of death. However, imatinib has positively altered the natural history. An observed 5-year survival rate of 80%, decreasing to 42% at 15 years, was noted in one retrospective study. In another series, the Mayo Clinic reported that, with long-term follow-up, the median survival was not reached and 18 of 22 (82%) were alive; however, 2 leukemic transformations were reported.

Management

The mainstay of therapy for patients with *PDGFRA*- and *PDGFRB*-related neoplasms is the use of imatinib. One of the earliest pivotal reports identifying *FIPL1-PDGRA* as a therapeutic target of imatinib was reported by Cools et al in 2003. Following this report, investigators from the National Institute of Health (NIH) reported on improved hematological parameters, including reversal of bone marrow fibrosis, along with molecular remissions in 5 of 6 patients. Subsequently, several single- and multi-institution studies have looked at the efficacy of low to conventional doses of imatinib for the treatment of *PDGFRA*-related neoplasms. These studies report remarkably similar results, in which patients with *PDGFRA* gene rearrangements have rapid, deep, and durable responses to low to conventional doses of imatinib (100 to 400 mg/d). Along these lines, the ELN reported the results of 11 patients treated for at least 12 months with imatinib. Overall, 11 of 11 evaluable patients achieved at least a 3-log reduction in *FIP1L1-PDGFRA* fusion transcripts, and 9 of 11 patients achieved a complete molecular remission. Similarly, an Italian multicenter study demonstrated high levels of durable (median, 25 months) and complete molecular remissions in 27 patients with *PDGFRA*-related neoplasms. In those with known eosinophilic heart disease, steroids are recommended concurrently with imatinib during the first 1 to 2 weeks of therapy given prior reports of cardiogenic shock.

Interestingly, in a retrospective report of 44 patients by the French Eosinophil Network, complete hematologic and molecular remission was obtained in 44 of 44 and 43 of 44, respectively. Among 11 patients in whom imatinib was discontinued, 5 remained in remission (range, 9 to 88 months). However, this strategy requires confirmation in a prospective setting, and indefinite therapy is recommended. Compared with *BCR-ABL1*-positive CML, kinase domain mutations that confer resistance to imatinib therapy, including T674I and D842V, are rare in *FIP1L1PDGRFA* rearrangement-positive disease. Other tyrosine-kinase inhibitors have been used in this setting with only modest and transient benefit.

In 2002, Apperley et al reported 4 patients with *PDGFRB*-related neoplasms treated with imatinib 400 mg daily. Normalization of blood accounts occurred within 4 weeks, the t(5;12) translocation was undetectable by 12 to 36 weeks, and transcript levels decreased in those with the *ETV6-PDGFRB* fusion. A report on 12 patients with *PDGFRB*-related neoplasms who received imatinib therapy for a median of 47 months revealed normalization of peripheral blood cell counts and disappearance of eosinophilia in 11; furthermore, 10 patients had complete resolution of cytogenetic abnormalities and decrease in or disappearance of fusion transcripts measured by RT-PCR. A retrospective report of an expanded cohort of 26 patients with a median follow-up of 10.2 years (imatinib duration, 6.6 years) reported a 90% 10-year survival, a 96% response rate, and that no patient with complete cytogenetic (N = 13) or molecular (N = 8) response lost their response.

Myeloid/lymphoid neoplasms with *FGFR1* rearrangement

This uncommon and heterogeneous group of neoplasms arise from pluripotent hematopoietic stem cells and are associated with rearrangements in the *FGFR1* gene and eosinophilia. Formerly known as 8p11 myeloproliferative syndrome or 8p11 stem cell syndrome, *FGFR1*-related neoplasms can present as classic MPNs, precursor B- or T-cell lymphoblastic leukemia, or AML. *FGFR1*-related neoplasms have been reported across a wide age range (3 to 84 years), and the median age of diagnosis is 32 years. Females constitute approximately 40% of the cases. It is important to note that eosinophilia is not always present despite the name of the diagnostic category.

Pathobiology

The molecular consequences of *FGFR1* rearrangements are remarkably well-described for such an uncommon neoplasm. The pathobiology of this disorder is described in the "Driver mutations" section of this chapter.

Clinical features and diagnosis

Clinical manifestations include fever, weight loss, and night sweats. Lymphadenopathy is common in patients with lymphomatous presentation. Hypercatabolism and splenomegaly are common features of AML and MPN patients. Diagnostic criteria outlined in the 2016 WHO classification include the presence of an MPN

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with prominent eosinophilia and occasional neutrophilia or monocytosis *or* the presence of AML or precursor B- or T-cell lymphoblastic leukemia *and* the presence of *FGFR1* rearrangement. The most common chromosomal translocation associated with *FGFR1*-related neoplasms is t(8;13) (p11;q12), which results in expression of the ZNF198-FGFR1 fusion TK. Fifteen fusion gene partners have been described in *FGFR1* rearrangement neoplasms, including *CEP110*, *FGFR1OP1*, *FGFR1OP2*, *TRIM 24*, *MYO18A*, *HERVK*, and *BCR*.

Course and prognosis

The prognosis for patients with *FGFR1*-related neoplasms is very poor, with evolution to AML typically occurring within 1 to 2 years. The clinical aggressiveness and diminished awareness about the features of this entity, and the lack of approved therapies, make the treatment of these patients very challenging.

Management

Early intensive chemotherapy followed by allogeneic stem cell transplant (SCT) remains the only potential curative therapy for patients with *FGFR1*-related neoplasms. Interestingly, midostaurin has demonstrated *in vitro* activity against one subtype of the *FGFR1* fusion gene and, in one patient, resulted in improved leukocytosis, splenomegaly, lymphadenopathy, and 6 months of clinical stability prior to transplantation. Additional TKIs with anti-*FGFR1* activity are being evaluated, including selective FGFR1 inhibitor pemigatinib that demonstrated impressive efficacy at the time of interim analysis. This study is ongoing (ClinicalTrials.gov: identifier NCT03011372).

Myeloid/lymphoid neoplasms with *PCM1-JAK2* rearrangement

A patient with t(8;9)(p22;p24) was described by Stewart et al in 1990, and the identification of the *PCM1-JAK2* fusion gene by Reiter et al followed in 2005. Across the more than 30 cases reported in the literature, there is a marked male predominance. The median age at the time of diagnosis is ~50 years. In addition to eosinophilia, hepatosplenomegaly is a common clinical feature. However, it is important to note that eosinophilia is not present in all cases. The bone marrow is often left-shifted with erythroid predominance and lymphoid aggregates. Many patients also are found to have myelofibrosis. It can also rarely present as acute T- or B-cell lymphoblastic leukemia. Myeloid or lymphoid neoplasms with t(8;9)(p22;p24.1);PCM1-JAK2 was added to the 2016 WHO diagnostic classification schema as a provisional entity.

Pathobiology

Several breakpoint locations affecting JAK2 and PCM1 have been identified in patients with t(8;9) that lead to a fusion product with the coiled-coil domains of PCM1 and the tyrosine-kinase domain of JAK2. The oligomerization of PCM1-JAK2 results in constitutive activation of JAK2.

Management

The prognosis for patients with *PCM1-JAK2*-related neoplasms is very poor, and evolution to AML typically occurs within 1 to 2 years. Two case reports have highlighted complete hematologic remissions and cytogenetic responses in patients with *PCM1-JAK2* treated with ruxolitinib. However, the duration of these remissions can be variable, and allogenic transplantation should be considered irrespective of response to ruxolitinib.

KEY POINTS

See Figures 17-8 and 17-9.

- CNL is characterized by a sustained mature and neutrophilic leukocytosis often with splenomegaly, and *CSF3R* mutations identified in substantial proportions of patients. CNL is a progressive MPN, with HU and allogeneic SCT as treatment options; although, TKI may have a future role depending on the type of *CSF3R* mutation that is present.
- Mastocytosis includes cutaneous and systemic mastocytosis; the latter is more commonly found in adults and includes both indolent and aggressive subtypes. Aggressive mastocytosis can be associated with an underlying hematological malignancy or can manifest as mast cell leukemia. Consequences stem from mediator release or organ infiltration, and most patients have *KIT* D816V mutations. Treatments are supportive, including a H_1/H_2 antihistamine blockade and mast cell stabilizers. Along with bisphosphonates, IFN is an option for patients with severe refractory bone involvement. Patients whose disease lacks the *KIT* 816V mutations are sensitive to imatinib, where midostaurin is an active agent independent of *KIT* mutation status.
- Myeloproliferative neoplasms with eosinophilia include CEL and those with *PDGFRA/PDGFRB*, *FGFR1*, and *PCM1-JAK2* rearrangements. Cardiac involvement can be a source of morbidity and mortality, especially in those with CEL and *PDGFRA*-rearranged disease. Characteristic findings include sustained eosinophilia, often with monocytosis in those with *PDGFRB*-rearranged disease. Those with *FGFR1* rearrangements may also have splenomegaly and lymphadenopathy. Patients with *PDGFRA/PDGFRB*-rearranged disease are uniquely sensitive to imatinib, which has had a very positive impact on prognosis for these rare neoplasms.

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Clinical features	Skin lesions: urticaria pigmentosa and Darier sign Constitutional and mediator release symptoms Anaphylaxis Osteopenia, fracture Hepatosplenomegaly			
Diagnostic criteria	*Major criterion*: Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow an/or extracutaneous organ(s) *Minor criteria*: a) >25% with atypia, immaturity, or spindle-shaped appearance b) Mast cell expression of CD117 with CD2 and/or CD25 c) *KIT* D816B d) Serum tryptase persistently >20 ng/mL			
Subtypes	**Indolent** No AHN No "C" findings	Advanced systemic mastocytosis		
		Aggressive SM No MCL ≥1 "C" finding (malabsorption, skeletal lesions, impaired liver function, splenomegaly, or cytopenias)	**SM-AHN** SM in addition to WHO criteria for AML, MDS, MPN, or lymphoma	**Mast cell leukemia** ≥10% neoplastic mast cells in blood or ≥20% on aspirate
Clinical features	Trigger avoidance H1/H2 blockers, proton pump inhibitors, leukotriene antagonists, cromolyn, IFNα			
	Clinical trial, midostaurin, cladribine, chemotherapy Allogeneic SCT			

Figure 17-8 Systemic mastocytosis is diagnosed in the presence of 1 major criterion and 1 minor criterion or in the presence of at least 3 minor criteria. See Table 17-17.

Figure 17-9 The hypereosinophilias discussed in this chapter are typically characterized by sustained eosinophilia and end-organ consequences, the most severe of which can be cardiac in nature. HES is distinguished by absence of a clonal marker, and steroids are considered a frontline therapeutic option. It is critical to recognize *PDGFRA*/*PDGFRB*-rearranged neoplasms given their remarkable sensitivity to low-dose imatinib. See the text for diagnostic criteria (Table 17-5).

Clinical and laboratory features	Cardiac, pulmonary, neurological, and dermatological involvement Splenomegaly Lymphadenopathy (*FGFR1*) Sustained eosinophilia (>1.5 × 10^9/L) Anemia, thrombocytopenia Bone marrow fibrosis				
Subtypes	HES	*PDGFRA*/*PDGFRB* and *FGFR1*-rearranged neoplasms or with *PCM1-JAK2*			CEL-NOS
Additional diagnostic features	Persistent, primary eosinophilia with end-organ damage; no increased blood/bone marrow blasts; no clonal disease or aberrant T-cell population	***PDGFRA***	***PDGFRB*** May have features in common with CMML, JMML, MDS/MPN-U, atypical CML	***FGFR1***	***PCM1-JAK2***	Clonal abnormality; blast cells <20% in the blood or bone marrow; lack of *BCR-ABL*, *PDGFRA*/*PDGFRB*, *FGFR1*, or *PCM1-JAK2* rearrangements
First-line treatment options	Steroids	Imatinib (initiate steroids if elevated cardiac troponin) and/or cardiac dysfunction	Clinical trial or induction chemotherapy followed by allogeneic transplantation		JAK2 inhibitor (ruxolitinib) followed by allogeneic transplantation	HU, IFNα, corticosteroids (if organ damage is present), empiric trial of imatinib, allogeneic transplantation

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